

INHIBITORS OF THE ICE/ced-3 FAMILY OF CYSTEINE PROTEASES

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent Application
5 No. 09/482,813, filed January 13, 2000 (which application is incorporated herein by
reference in its entirety).

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel classes of compounds which are
10 inhibitors of interleukin-1 β converting enzyme and related proteases ("ICE/ced-3 family of
cysteine proteases"), as well as pharmaceutical compositions comprising these compounds
and to methods of using such pharmaceutical compositions.

Description of the Related Art

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory
15 protein that stimulates fibroblast differentiation and proliferation, the production of
prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil
and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al.,
Immunology Today 7:45-56 (1986). As such, it is involved in the pathogenesis of chronic
and acute inflammatory and autoimmune diseases. IL-1 is predominantly produced by
20 peripheral blood monocytes as part of the inflammatory response. Mosely, B.S. et al.,
Proc. Nat. Acad. Sci. 84:4572-4576 (1987); Lonnemann, G. et al., *Eur. J. Immunol.*
19:1531-1536 (1989).

IL-1 β is synthesized as a biologically inactive precursor, proIL-1 β . ProIL-1 β
is cleaved by a cysteine protease called interleukin-1 β converting enzyme ("ICE") between
25 Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in

human serum and synovial fluid. Sleath, P.R. et al., *J. Biol. Chem.* 265:14526-14528 (1992); A.D. Howard et al., *J. Immunol.* 147:2964-2969 (1991).

ICE is a cysteine protease localized primarily in monocytes. In addition to promoting the pro-inflammatory and immunoregulatory properties of IL-1 β , ICE, and particularly its homologues, also appear to be involved in the regulation of cell death or apoptosis. Yuan, J. et al., *Cell* 75:641-652 (1993); Miura, M. et al., *Cell* 75:653-660 (1993); Nett-Giordalisi, M.A. et al., *J. Cell Biochem.* 17B:117 (1993). In particular, ICE or ICE/ced-3 homologues are thought to be associated with the regulation of apoptosis in neurogenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, *Science* 259:760-762 (1993); Gagliardini, V. et al., *Science* 263:826-828 (1994).

Thus, disease states in which inhibitors of the ICE/ced-3 family of cysteine proteases may be useful as therapeutic agents include: infectious diseases, such as meningitis and salpingitis; septic shock, respiratory diseases; inflammatory conditions, such as arthritis, cholangitis, colitis, encephalitis, endocerositis, hepatitis, pancreatitis and reperfusion injury, ischemic diseases such as the myocardial infarction, stroke and ischemic kidney disease; immune-based diseases, such as hypersensitivity; auto-immune diseases, such as multiple sclerosis; bone diseases; and certain neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Such inhibitors are also useful for the repopulation of hematopoietic cells following chemo- and radiation therapy and for prolonging organ viability for use in transplantation.

ICE/ced-3 inhibitors represent a class of compounds useful for the control of the above-listed disease states. Peptide and peptidyl inhibitors of ICE have been described. However, such inhibitors have been typically characterized by undesirable pharmacologic properties, such as poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in *Drug Discovery Technologies*, C.R. Clark and W.H. Moos, Eds. (Ellis-Horwood, Chichester, England, 1990), pp. 92-126. These undesirable properties have hampered their development into effective drugs.

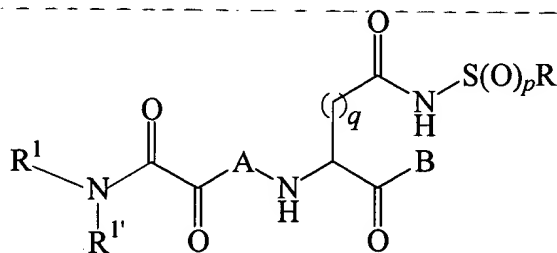
Accordingly, the need exists for compounds that can effectively inhibit the action of the ICE/ced-3 family of proteases, for use as agents for preventing unwanted

apoptosis, and for treating chronic and acute forms of IL-1 mediated diseases such as inflammatory, autoimmune or neurodegenerative diseases. The present invention satisfies this need and provides further related advantages.

SUMMARY OF THE INVENTION

In general, the compounds of this invention incorporate a sulfonamido (NHSO₂) or sulfinamido (NHSO) modified (N-substituted)oxamyl group as a dipeptide mimetic. The resulting compounds exhibit improved properties relative to their peptidic counterparts, for example, such as improved cell penetration or improved absorption and metabolic stability resulting in enhanced bioavailability.

One aspect of the instant invention is the compounds of the following Formula I:



Formula I

wherein A, B, R, R', p and q are as defined below, as well as pharmaceutically acceptable salts thereof.

A further aspect of the instant invention is a pharmaceutical composition comprising a compound of the above Formula I and a pharmaceutically-acceptable carrier therefor.

Another aspect of this invention involves a method for treating an autoimmune disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

Yet another aspect of the instant invention is a method for treating an inflammatory disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

A further aspect of the instant invention is a method for treating a neurodegenerative disease comprising administering an effective amount of a pharmaceutical composition discussed above to a patient in need of such treatment.

Another aspect of the instant invention is a method of preventing ischemic injury to a patient suffering from a disease associated with ischemic injury comprising administering an effective amount of the pharmaceutical composition discussed above to a patient in need of such treatment.

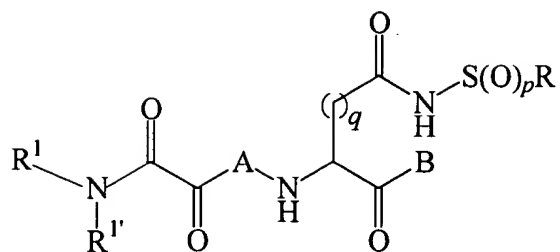
A further aspect of the instant invention is a method for expanding of hematopoietic cell populations and/or enhancing their survival by contacting the cells with an effective amount of the pharmaceutical composition discussed above. Cell populations included in the method of the invention include (but are not limited to) granulocytes, monocytes, erythrocytes, lymphocytes and platelets for use in cell transfusions.

An alternate aspect of the instant invention is a method of prolonging the viability of an organ that has been removed from the donor for the purpose of a future transplantation procedure, which comprises applying an effective amount of the pharmaceutical composition discussed above to the organ, thereby prolonging the viability of the organ as compared to an untreated organ. The organ may be an intact organ, or isolated cells derived from an organ (e.g., isolated pancreatic islet cells, isolated dopaminergic neurons, blood or hematopoietic cells).

These and other aspects of this invention will be evident upon reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

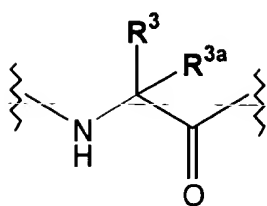
As mentioned above, one aspect of the instant invention is the compounds of the Formula I:



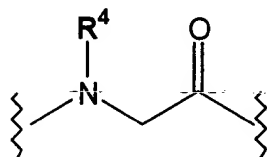
Formula I

wherein:

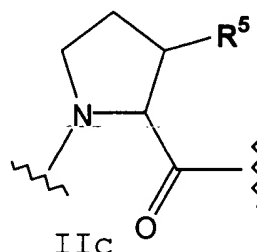
A is a natural or unnatural amino acid of Formula IIa-i:



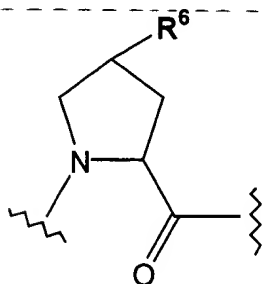
IIa



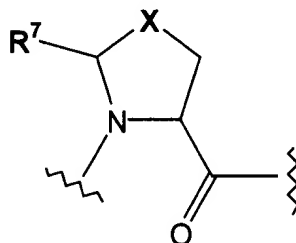
IIb



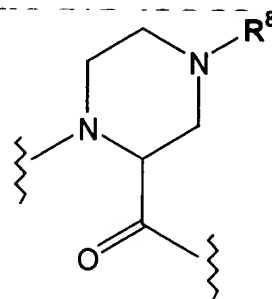
IIc



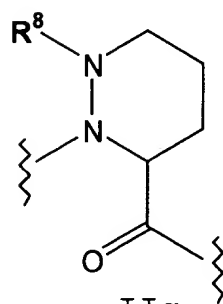
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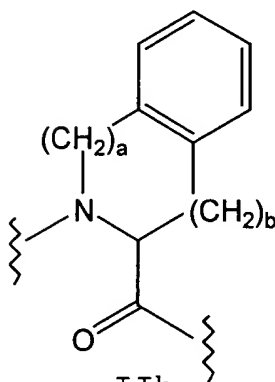
IIe



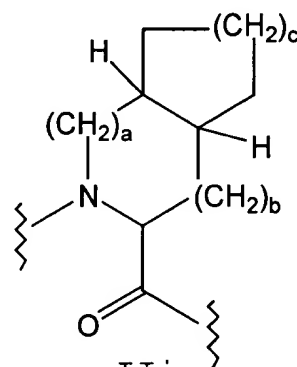
IIIf



IIIG



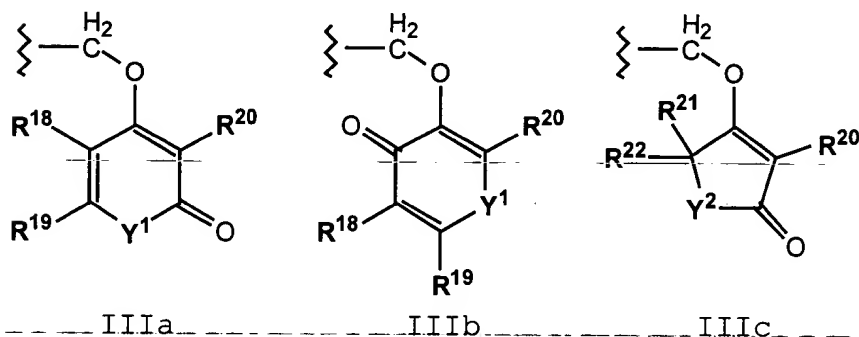
IIH



IIIi

B is a hydrogen atom, a deuterium atom, alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, 2-benzoxazolyl, substituted 2-oxazolyl, $(CH_2)_n$ cycloalkyl,

(CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), (CH₂)_n(substituted 1 or 2-naphthyl), (CH₂)_n(heteroaryl), (CH₂)_n(substituted heteroaryl), halomethyl, CO₂R¹², CONR¹³R¹⁴, CH₂ZR¹⁵, CH₂OCO(aryl), CH₂OCO(heteroaryl), or CH₂OPO(R¹⁶)R¹⁷, where Z is an oxygen or a sulfur atom, or B is a group of the Formula IIIa-c:



p is 1 or 2;

q is 1 or 2;

R and R¹ are the same or different and independently alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heterocycle, substituted heterocycle, (heterocycle)alkyl, substituted (heterocycle)alkyl, R^{1a}(R^{1b})N or R^{1c}O;

R^{1'} is hydrogen, alkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, heterocycle or substituted heterocycle;

or R¹ and R^{1'} taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle;

and wherein:

R^{1a} and R^{1b} are the same or different and, at each occurrence, independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl,

substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl, with the proviso that R^{1a} and R^{1b} cannot both be hydrogen;

5

R^{1c} is, at each occurrence, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heteroaryl, substituted heteroaryl, (heteroaryl)alkyl, or substituted (heteroaryl)alkyl;

10

R³ is lower alkyl, cycloalkyl, phenyl, substituted phenyl, (CH₂)_nNH₂, (CH₂)_nNHCOR⁹, (CH₂)_nN(C=NH)NH₂, (CH₂)_mCO₂R², (CH₂)_mOR¹⁰, (CH₂)_mSR¹¹, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl) or (CH₂)_n(heteroaryl), wherein heteroaryl includes pyridyl, thienyl, furyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, pyrazinyl, pyrimidyl, triazinyl, tetrazolyl, and indolyl;

15

R^{3a} is hydrogen or methyl, or R³ and R^{3a} taken together are -(CH₂)_d- where d is an integer from 2 to 6;

20

R⁴ is phenyl, substituted phenyl, (CH₂)_mphenyl, (CH₂)_m(substituted phenyl), cycloalkyl, or benzofused cycloalkyl;

R⁵ is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

25

R⁶ is hydrogen, fluorine, oxo, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), OR¹⁰, SR¹¹ or NHCOR⁹;

R⁷ is hydrogen, oxo (*i.e.*, = O), lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl,

(CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R⁸ is lower alkyl, cycloalkyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), or COR⁹;

R⁹ is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), OR¹², or NR¹³R¹⁴;

R¹⁰ is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹¹ is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹² is lower alkyl, cycloalkyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹³ is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹⁴ is hydrogen or lower alkyl;

or R¹³ and R¹⁴ taken together form a five to seven membered carbocyclic or heterocyclic ring, such as morpholine, or N-substituted piperazine;

R¹⁵ is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), or (CH₂)_n(heteroaryl);

R¹⁶ and R¹⁷ are independently lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl;

R¹⁸ and R¹⁹ are independently hydrogen, alkyl, phenyl, substituted phenyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or R¹⁸ and R¹⁹ taken together are -(CH=CH)₂-;

R²⁰ is hydrogen, alkyl, phenyl, substituted phenyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl);

R²¹, R²² and R²³ are independently hydrogen, or alkyl;

X is CH₂, (CH₂)₂, (CH₂)₃, or S;

Y¹ is O or NR²³;

Y² is CH₂, O, or NR²³;

a is 0 or 1 and b is 1 or 2, provided that when a is 1 then b is

1;

c is 1 or 2, provided that when c is 1 then a is 0 and b is 1;

m is 1 or 2; and

n is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

As used herein, the term "alkyl" means a straight or branched C₁ to C₁₀ carbon chain, such as methyl, ethyl, tert-butyl, iso-propyl, n-octyl, and the like. The term "lower alkyl" means a straight chain or branched C₁ to C₆ carbon chain, such as methyl, ethyl, iso-propyl, and the like.

The term "cycloalkyl" means a mono-, bi-, or tricyclic ring that is either fully saturated or partially unsaturated. Examples of such a ring include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, cis- or trans decalin, bicyclo[2.2.1]hept-2-ene, cyclohex-1-enyl, cyclopent-1-enyl, 1,4-cyclooctadienyl, and the like.

The term "(cycloalkyl)alkyl" means the above-defined alkyl group substituted with one of the above cycloalkyl rings. Examples of such a group include

(cyclohexyl)methyl, 3-(cyclopropyl)-n-propyl, 5-(cyclopentyl)hexyl, 6-(adamantyl)hexyl, and the like.

The term "substituted phenyl" specifies a phenyl group substituted with one or more substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, trifluoromethyl, alkyl, alkoxy, acyl, acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(lower alkyl)carboxamide, protected N-(lower alkyl)carboxamide, N,N-di(lower alkyl)carboxamide, N-((lower alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or by a substituted or unsubstituted phenyl group, such that in the latter case a biphenyl or naphthyl group results, or wherein two adjacent alkyl substituents on the substituted phenyl ring taken together form a cycloalkyl to yield, for example, tetrahydronaphthyl or indanyl.

Examples of the term "substituted phenyl" includes a mono-, di-, tri-, tetra- or penta(halo)phenyl group such as 2-, 3- or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3- or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-, 3- or 4-fluorophenyl, 2,4,6-trifluorophenyl, 2,3,5,6-tetrafluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,4,5,6-pentafluorophenyl, and the like; a mono or di(hydroxy)phenyl group such as 2-, 3-, or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2-, 3-, or 4-nitrophenyl; a cyanophenyl group, for example, 2-,3- or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2-, 3-, or 4-methylphenyl, 2,4-dimethylphenyl, 2-, 3- or 4-(iso-propyl)phenyl, 2-, 3-, or 4-ethylphenyl, 2-, 3- or 4-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 2,6-dimethoxyphenyl, 2-, 3- or 4-(iso-propoxy)phenyl, 2-, 3- or 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2-, 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2-, 3- or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2-, 3- or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a

mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-, 3- or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the
5 substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like.

The term "phenylalkyl" means one of the above phenyl groups attached to one of the above-described alkyl groups, and the term "substituted phenylalkyl" means that
10 either the phenyl or the alkyl, or both, are substituted with one or more of the above-defined substituents. Examples of such groups include 2-phenyl-1-chloroethyl, 2-(4'-methoxyphenyl)ethyl, 4-(2',6'-dihydroxy phenyl)n-hexyl, 2-(5'-cyano-3'-methoxyphenyl)n-pentyl, 3-(2',6'-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4'-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4'-aminomethylphenyl)-3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-
15 pent-1-yl, (4-hydroxynaphth-2-yl)methyl, and the like.

The term "substituted naphthyl" means a naphthyl group substituted with one or more of the above-identified substituents, and the term "(1 or 2 naphthyl)alkyl" means a naphthyl (1 or 2) attached to one of the above-described alkyl groups.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo
20 groups. These terms may also be used to describe one or more halogens, which are the same or different. Preferred halogens in the context of this invention are chloro and fluoro.

The term "aryl" refers to aromatic five and six membered carbocyclic rings. Six membered rings are preferred.

The term "heteroaryl" denotes optionally substituted aromatic
25 five-membered or six-membered heterocyclic rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen atoms, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms.

The following ring systems are representative examples of the heterocyclic radicals denoted by the term "heteroaryl" (whether substituted or unsubstituted): thienyl,

furyl, pyrrolyl, pyrrolidinyl, imidazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, triazinyl, thiadiazinyl, tetrazolo, 1,5-[b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example, benzoxazolyl, benzothiazolyl, benzimidazolyl and indolyl.

- 5 The term "heterocycle" (also referred to herein as a "heterocycle ring") means a 5- to 7-membered monocyclic heterocyclic ring that is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. The
- 10 heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl,
- 15 tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

The terms "heteroarylalkyl" and "heterocyclealkyl" mean an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl, such as -CH₂thienyl and the like, or with a heterocycle, such as -CH₂morpholinyl and the like, respectively.

- Substituents for the above optionally substituted heteroaryl and heterocycle
- 20 rings are from one to three halo, trihalomethyl, amino, protected amino, amino salts, mono-substituted amino, di-substituted amino, carboxy, protected carboxy, carboxylate salts, hydroxy, protected hydroxy, salts of a hydroxy group, lower alkoxy, lower alkylthio, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, (cycloalkyl)alkyl, substituted (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, and substituted
- 25 phenylalkyl groups.

Substituents for the heteroaryl and heterocycle group are as defined above, or as set forth below. As used in conjunction with the above substituents for heteroaryl and heterocycle rings, "trihalomethyl" can be trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl, "lower alkoxy" means a C₁ to C₄ alkoxy group, similarly, "lower

alkylthio" means a C₁ to C₄ alkylthio group. The term "substituted lower alkyl" means the above-defined lower alkyl group substituted from one to three times by a hydroxy, protected hydroxy, amino, protected amino, cyano, halo, trifluoromethyl, mono-substituted amino, di-substituted amino, lower alkoxy, lower alkylthio, carboxy, protected carboxy, or a carboxy, amino, and/or hydroxy salt.

As used in conjunction with the substituents for the heteroaryl and heterocycle rings, the terms "substituted (cycloalkyl)alkyl" and "substituted cycloalkyl" are as defined above substituted with the same groups as listed for a "substituted alkyl" group. The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, alkyl, substituted alkyl, C₁ to C₇ acyl, C₂ to C₇ alkenyl, C₂ to C₇ substituted alkenyl, C₂ to C₇ alkynyl, C₇ to C₁₆ alkylaryl, C₇ to C₁₆ substituted alkylaryl and heteroaryl group. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino." The term "(disubstituted)amino" refers to amino groups with two substituents chosen from the group consisting of phenyl, substituted phenyl, alkyl, substituted alkyl, C₁ to C₇ acyl, C₂ to C₇ alkenyl, C₂ to C₇ alkynyl, C₇ to C₁₆ alkylaryl, C₇ to C₁₆ substituted alkylaryl and heteroaryl. The two substituents can be the same or different. The term "heteroaryl(alkyl)" denotes an alkyl group as defined above, substituted at any position by a heteroaryl group, as above defined.

Furthermore, the above optionally substituted five-membered or six-membered heterocyclic rings, and the above cycloalkyl rings, can optionally be fused to a aromatic 5-membered or 6-membered aryl or heteroaryl ring system. For example, the rings can be optionally fused to an aromatic 5-membered or 6-membered ring system such as a pyridine or a triazole system, and preferably to a benzene ring.

The term "pharmaceutically-acceptable salt" encompasses those salts that form with the carboxylate anions and includes salts formed with the organic and inorganic cations such as those chosen from the alkali and alkaline earth metals, (for example, lithium, sodium, potassium, magnesium, barium and calcium); and ammonium ion; and the organic cations (for example, dibenzylammonium, benzylammonium, 2-

hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzyl-ammonium, dibenzylethylenediammonium, and like cations.) Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine, and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. A preferred cation for the carboxylate anion is the sodium cation. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and includes organic or inorganic acids. Such acids include hydrochloric, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and the like acids.

The compounds of Formula I may also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyl dimethylsilyl, phenacyl, 2,2,2-trichloroethyl, β -(trimethylsilyl)ethyl, β -(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonyl ethyl, 4-nitrobenzylsulfonyl ethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in

C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A
5 related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl (THP), 2-methoxyprop-2-yl, 1-ethoxyeth-1-yl, methoxymethyl, β -methoxyethoxymethyl, methylthiomethyl, t-butyl,
10 t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4''-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl, and the like.

Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M.
15 Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. A preferred hydroxy-protecting group is the tetrahydropyranyl (THP) group. The related term "protected hydroxy" denotes a hydroxy group bonded to one of the above hydroxy-protecting groups.

The term "amino-protecting group" as used herein refers to substituents of
20 the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom.

Examples of such amino-protecting groups include the formyl ("For") group,
25 the trityl group, the phthalimido group, the trichloroacetyl group, the trifluoroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type-protecting groups, such as t-butoxycarbonyl ("Boc"), 2-(4-biphenyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl, 1,1-diphenylpropyl-1-

oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(*p*-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyl-oxycarbonyl, cyclohexanyloxy-carbonyl, 1-methyl-cyclohexanyloxy-carbonyl, 2-methylcyclohexanyl-oxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-
5 (triphenylphosphino)-ethoxycarbonyl, 9-fluorenyl-methoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyl-oxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyl-oxycarbonyl ("Cbz"), 4-
10 phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, α -2,4,5,-tetramethylbenzyl-oxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyl-oxycarbonyl, 4-chlorobenzyl-oxycarbonyl, 3-chlorobenzyl-oxycarbonyl, 2-chlorobenzyl-oxycarbonyl, 2,4-dichlorobenzyl-oxycarbonyl, 4-bromobenzyl-oxycarbonyl, 3-bromobenzyl-oxycarbonyl, 4-nitrobenzyl-oxycarbonyl, 4-cyanobenzyl-oxycarbonyl, 4-(decyloxy)benzyl-oxycarbonyl and
15 the like; the benzoylmethylsulfonyl group, the 2,2,5,7,8-pentamethylchroman-6-sulfonyl group ("PMC"), the dithiasuccinoyl ("Dts") group, the 2-(nitro)phenyl-sulfonyl group ("Nps"), the diphenylphosphine oxide group, and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the
20 appropriate point without disrupting the remainder of the molecule. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky,
25 "Principles of Peptide Synthesis," 1st and 2nd revised Ed., Springer-Verlag, New York, NY, 1984 and 1993, and J.M. Stewart and J.D. Young, "Solid Phase Peptide Synthesis," 2nd Ed., Pierce Chemical Co., Rockford, IL, 1984, E. Atherton and R.C. Shephard, "Solid Phase Peptide Synthesis - A Practical Approach" IRL Press, Oxford, England (1989), each

of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The terms "natural and unnatural amino acid" refers to both the naturally occurring amino acids and other non-proteinogenic α -amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxyglutamic acid, arginine, ornithine and lysine. Examples of unnatural α -amino acids include hydroxylysine, citrulline, kynurenine, (4-aminophenyl)alanine, 3-(2'-naphthyl)alanine, 3-(1'-naphthyl)alanine, methionine sulfone, (t-butyl)alanine, (t-butyl)glycine, 4-hydroxyphenyl-glycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, thyronine, 6-hydroxytryptophan, 5-hydroxytryptophan, 3-hydroxy-kynurenine, 3-aminotyrosine, trifluoromethylalanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)cysteine, 3,4-dimethoxy-phenylalanine, 3-(2'-thiazolyl)alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-(trifluoromethylphenyl)alanine, (cyclohexyl)glycine, thiohistidine, 3-methoxytyrosine, norleucine, norvaline, alloisoleucine, homoarginine, thioproline, dehydro-proline, hydroxyproline, homoproline, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, α -amino-n-butyric acid, cyclohexylalanine, 2-amino-3-phenylbutyric acid, phenylalanine substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following groups: a (C_1 to C_4)alkyl, a (C_1 to C_4)alkoxy, a halogen or a nitro group, or substituted once with a methylenedioxy group; β -2- and 3-thienylalanine; β -2- and 3-furanylalanine; β -2-, 3- and 4-pyridylalanine; β -(benzothienyl-2- and 3-yl)alanine; β -(1- and 2-naphthyl)alanine; O-alkylated derivatives of serine, threonine or tyrosine; S-alkylated cysteine, S-alkylated homocysteine, the O-sulfate, O-phosphate and O-carboxylate esters of tyrosine; 3-(sulfo)tyrosine, 3-(carboxy)tyrosine, 3-(phospho)tyrosine, the 4-methane-sulfonic acid ester of tyrosine,

4-methanephosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitrotyrosine, ϵ -alkyllysine, and delta-alkyl ornithine. Any of these α -amino acids may be substituted with a methyl group at the alpha position, a halogen at any position of the aromatic residue on the α -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are discussed above.

The compounds of this invention may be modified by appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (*e.g.*, blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of exertion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Some examples of pro-drug forms include ketal, acetal, oxime, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the group denoted as "A" in Formula I or the modified aspartic acid residue attached to the group denoted as "A".

With regard to the p and q groups of Formula I, typical embodiments include compounds wherein q is 1 and p is 2.

Compounds of this invention with respect to the R, R¹ and R^{1'} groups in Formula I, include those wherein:

R is lower alkyl;

R¹ is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, or (heteroaryl)alkyl; and

R^{1'} is hydrogen or lower alkyl.

More typically, the compounds of this invention with respect to the R, R¹, and R^{1'} groups include those wherein:

R is methyl;

R^1 is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, or (1 or 2 naphthyl)alkyl; and

$R^{1'}$ is hydrogen.

Compounds of this invention with respect to the A group in Formula I, include those of Formula IIa wherein:

R^3 is lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, or $(CH_2)_n(1\ or\ 2-naphthyl)$;

R^{3a} is hydrogen;

R^{10} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, or $(CH_2)_n(1\ or\ 2-naphthyl)$;

R^{11} is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, or $(CH_2)_n(1\ or\ 2-naphthyl)$; and

$n = 1-4$ and $m = 1$ or 2 .

Compounds of this invention with respect to the A group in Formula I also include those of Formula IIb wherein:

R^4 is phenyl, substituted phenyl, $(CH_2)_mphenyl$, $(CH_2)_m(substituted\ phenyl)$, cycloalkyl, or 2-indanyl; and

$m = 1$ or 2 .

Another group of compounds with respect to the A group in Formula I include those of Formula IIc wherein:

R^6 is hydrogen, fluorine, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, $(CH_2)_n(1\ or\ 2-naphthyl)$, OR^{10} , or SR^{11} ;

R^{10} and R^{11} are independently cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, or $(CH_2)_n(1\ or\ 2-naphthyl)$; and

n = 1-4.

A fourth group of compounds with respect to the A group in Formula I include those of Formula IIe wherein:

5 R^7 is hydrogen, oxo, cycloalkyl, phenyl, substituted phenyl, or naphthyl; and

$X = CH_2, (CH_2)_2, (CH_2)_3, \text{ or } S.$

Another group of compounds with respect to the A group in Formula I include those of Formula IIh wherein:

a = 0 and b = 1 or 2.

10 Compounds of this invention with respect to the B group in Formula I include those wherein:

B is hydrogen, 2-benzoxazolyl, substituted 2-oxazolyl, CH_2ZR^{15} , $CH_2OCO(aryl)$, or $CH_2OPO(R^{16})R^{17}$, where Z is an oxygen or a sulfur atom;

15 R^{15} is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, $(CH_2)_n(1\ or\ 2-naphthyl)$, or $(CH_2)_n(heteroaryl)$; and

R^{16} and R^{17} are independently alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl.

20 Another group of compounds with respect to the B group in Formula I include those of Formula IIIa-c wherein:

Y^1 is O or NR^{23} ;

Y^2 is CH_2 , O, or NR^{23} ;

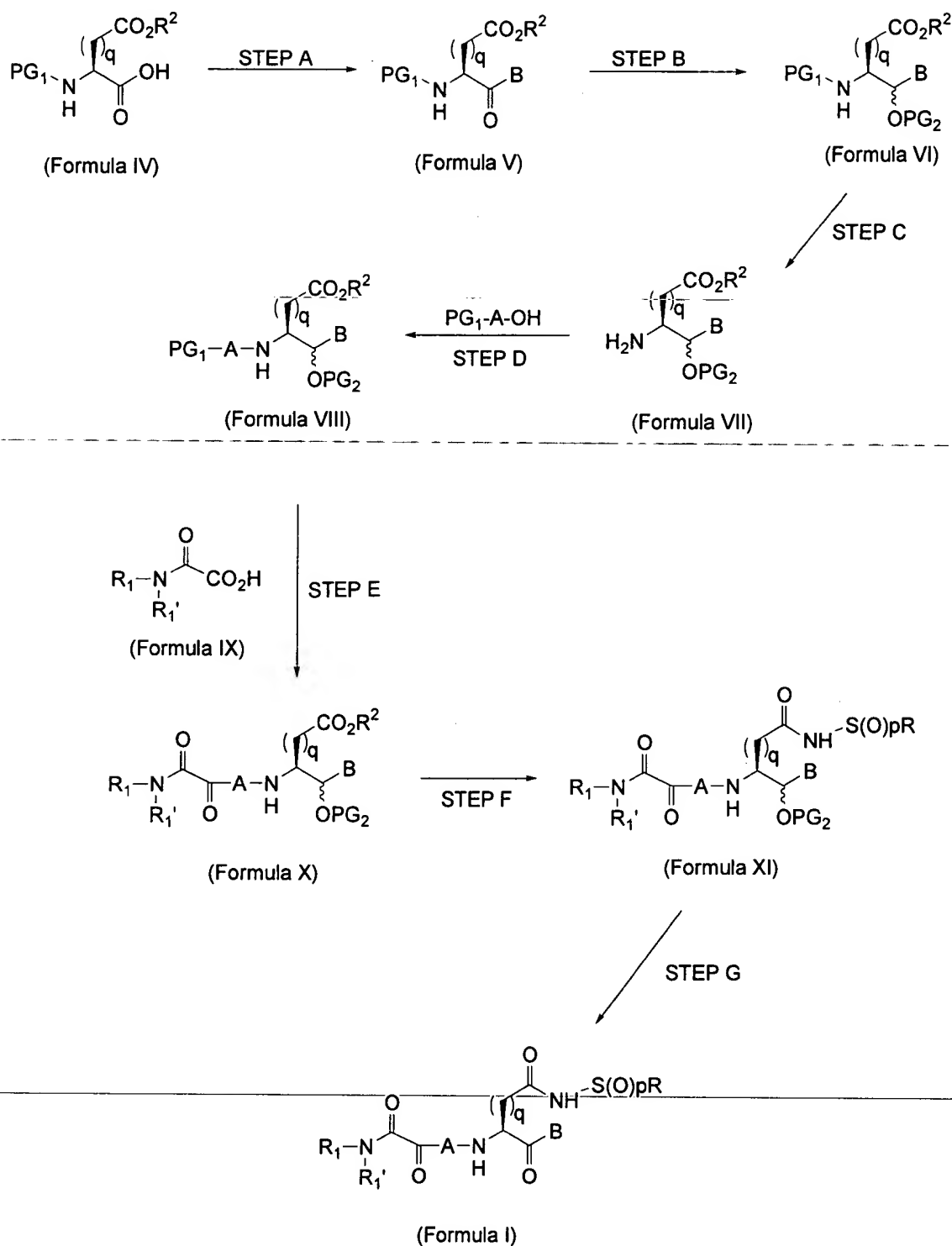
R^{18} and R^{19} are independently hydrogen, alkyl, or phenyl, or R^{18} and R^{19} taken together are $-(CH=CH)_2-$;

25 R^{20} is hydrogen, alkyl, phenyl, substituted phenyl, $(CH_2)_nphenyl$, or $(CH_2)_n(substituted\ phenyl)$; and

R^{21} , R^{22} and R^{23} are independently hydrogen or alkyl.

The compounds of Formula I may be synthesized using conventional techniques, as well as by the following Reaction Schemes.

Reaction Scheme 1



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In the above Reaction Scheme 1, R^2 represents hydrogen or a carboxy protecting group, wherein the carboxy protecting group is as defined above. "PG₁" stands for an amino protecting group, "PG₂" stands for a hydroxy-protecting group, and "A" stands for a natural or unnatural amino acid of formula IIa through IIi, as discussed above.

5 The modified aspartic acids of Formula V can be prepared by methods well known in the art. See, for example, European Patent Application 519,748; PCT Patent Application No. PCT/EP92/02472; PCT Patent Application No. PCT/US91/06595; PCT Patent Application No. PCT/US91/02339; European Patent Application No. 623,592; World Patent Application No. WO 93/09135; PCT Patent Application No. PCT/US94/08868; European Patent Application No. 623,606; European Patent Application No. 618,223; European Patent Application No. 533,226; European Patent Application No. 528,487; European Patent Application No. 618,233; PCT Patent Application No. PCT/EP92/02472; World Patent Application No. WO 93/09135; PCT Patent Application No. PCT/US93/03589; and PCT Patent Application No. PCT/US93/00481, all of which are
10 herein incorporated by reference. For example, in Step A, the carboxylic acid moiety of Formula IV is converted to its bromomethyl ketone which is then treated with either $R^{15}Z-H$, (aryl)-CO₂H, (heteroaryl)-CO₂H, or $R^{16}(R^{17})PO_2H$ in the presence of an inorganic base such as potassium carbonate or potassium fluoride in an inert solvent such as dimethyl formamide to give the corresponding intermediate of Formula V in which B is CH₂ZR¹⁵,
15 CH₂OCO(aryl), CH₂OCO(heteroaryl), or CH₂OPO(R¹⁶)R¹⁷, respectively.
20

Reduction of the carbonyl group in Formula V (Step B) with a hydride reducing agent such as sodium borohydride gives rise to a diastereomeric mixture of alcohols which are further protected with a hydroxy-protecting group (PG₂) as referenced above.

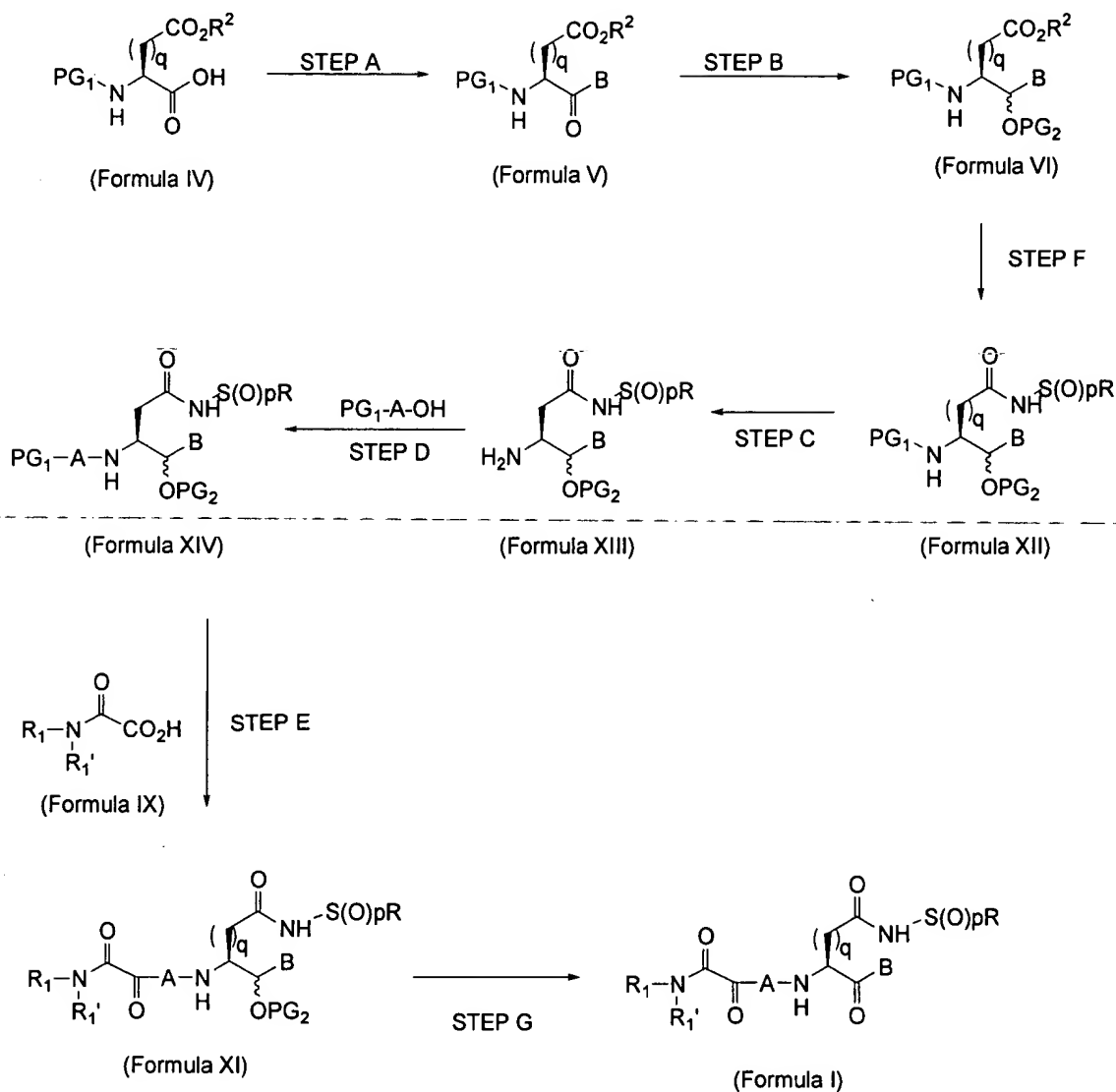
25 The coupling reaction carried out under Step D is performed in the presence of a standard peptide coupling agent such as the combination of the combination of dicyclohexylcarbodiimide(DCC) and 1-hydroxy-benzotriazole(HOBt), as well as the BOP (benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate) reagent, pyBOP (benzotriazolyloxy-tris(N-pyrrolidiny)phosphoniumhexafluorophosphate), HATU

5 (O-7-Azabenzotriazol-1-yl-tetramethylisouronium-hexafluorophosphate), HBTU (O-benzotriazolyl-tetramethylisouronium-hexafluorophosphate), and EEDQ (1-ethyloxycarbonyl-2-ethoxy-1,2-dihydroquinoline) reagents, the combination of 1-ethyl(3,3'-dimethyl-1'-aminopropyl)carbodiimide (EDAC) and HOBt, and the like, as discussed in J. Jones, "Amino Acid and Peptide Synthesis," Steven G. Davis ed., Oxford University Press, Oxford, pp. 25-41 (1992); M. Bodanzky, "Principles of Peptide Synthesis," Hafner et al. ed., Springer-Verlag, Berlin Heidelberg, pp. 9-52 and pp. 202-251 (1984); M. Bodanzky, "Peptide Chemistry, A Practical Textbook," Springer-Verlag, Berlin Heidelberg, pp. 55-73 and pp. 129-180; and Stewart and Young, "Solid Phase Peptide
10 Synthesis," Pierce Chemical Company, (1984), all of which are herein incorporated by reference. The amino protecting group is then removed and the resulting amine is coupled to the (N-substituted) oxamic acid of Formula IX (Step E). Again, this coupling reaction uses the standard peptide coupling reactions mentioned above.

15 Conversion of the carboxylate of Formula X to the acyl sulfonamide (Step F) involves removal of the carboxy protecting group (R_2) using standard conditions well known in the art. The resulting carboxylic acid is then treated with CDI (2 eq.) in THF at room temperature for 3 hours, followed by $H_2NS(O)_qR$ (2 eq.) in DBU (2 eq.) at room temperature for 4 hours.

20 The acyl sulfonamide intermediate of Formula XI is reacted in Step G with TsOH (0.4 eq.) in methanol at room temperature for 30 minutes to de-protect the alcohol, which may be converted to the corresponding carbonyl of Formula I by employing the Dess-Martin periodinane reagent and DCM at room temperature for 30 minutes.

Reaction Scheme 2



In the above Reaction Scheme 2, R^2 represents hydrogen or a carboxy protecting group, wherein the carboxy protecting group is as defined above. "PG₁" stands for an amino protecting group, "PG₂" stands for a hydroxy-protecting group, and "A" stands for a natural or unnatural amino acid of formula IIa through IIi, as discussed above.

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The modified aspartic acids of Formula V can be prepared by methods well known in the art. See, for example, European Patent Application 519,748; PCT Patent Application No. PCT/EP92/02472; PCT Patent Application No. PCT/US91/06595; PCT Patent Application No. PCT/US91/02339; European Patent Application No. 623,592; 5 World Patent Application No. WO 93/09135; PCT Patent Application No. PCT/US94/08868; European Patent Application No. 623,606; European Patent Application No. 618,223; European Patent Application No. 533,226; European Patent Application No. 528,487; European Patent Application No. 618,233; PCT Patent Application No. PCT/EP92/02472; World Patent Application No. WO 93/09135; PCT Patent Application 10 No. PCT/US93/03589; and PCT Patent Application No. PCT/US93/00481, all of which are herein incorporated by reference. For example, in Step A, the carboxylic acid moiety of Formula IV is converted to its bromomethyl ketone which is then treated with either $R^{15}Z-H$, (aryl)-CO₂H, (heteroaryl)-CO₂H, or $R^{16}(R^{17})PO_2H$ in the presence of an inorganic base such as potassium carbonate or potassium fluoride in an inert solvent such as dimethyl 15 formamide to give the corresponding intermediate of Formula V in which B is CH₂ZR¹⁵, CH₂OCO(aryl), CH₂OCO(heteroaryl), or CH₂OPO(R¹⁶)R¹⁷, respectively.

Reduction of the carbonyl group in Formula V (Step B) with a hydride reducing agent such as sodium borohydride gives rise to a diastereomeric mixture of alcohols which are further protected with a hydroxy-protecting group (PG₂) as referenced 20 above.

Conversion of the carboxylate of Formula VI to the acyl sulfonamide (Step F) involves removal of the carboxy protecting group (R₂) using standard conditions well known in the art. The resulting carboxylic acid is then treated with CDI (2 eq.) in THF at room temperature for 3 hours, followed by H₂NS(O)_pR (2 eq.) in DBU (2 eq.) at room 25 temperature for 4 hours.

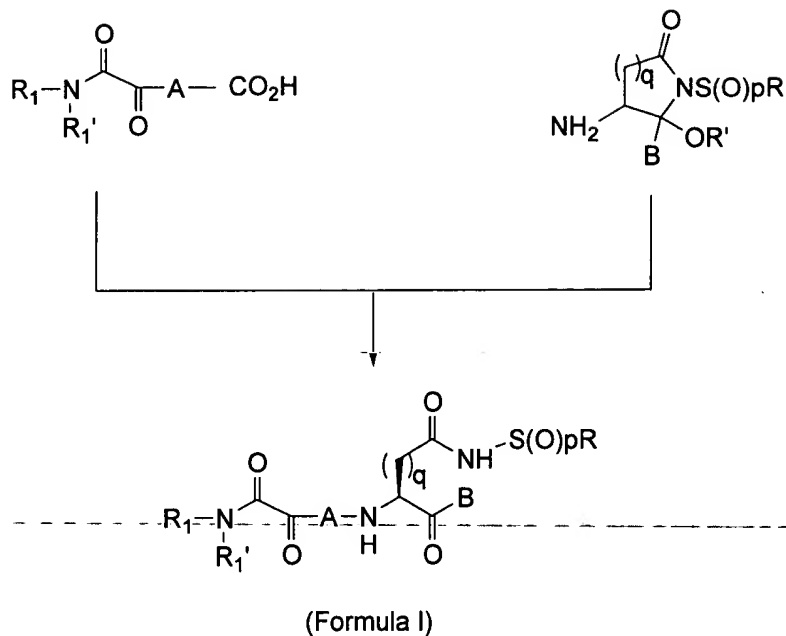
The coupling reaction carried out under Step D is performed in the presence of a standard peptide coupling agent such as the combination of the combination of dicyclohexylcarbodiimide(DCC) and 1-hydroxy-benzotriazole(HOBt), as well as the BOP (benzotriazolyloxy-tris-(dimethylamino)phosphonium hexafluorophosphate) reagent,

pyBOP (benzotriazolyloxy-tris(N-pyrolidiny)phosphoniumhexafluorophosphate), HATU (O-7-Azabenzotriazol-1-yl-tetramethylisouronium-hexafluorophosphate), HBTU (O-benzotriazolyly-tetramethylisouronium-hexafluorophosphate), and EEDQ (1-ethyloxycarbonyl-2-ethyloxy-1,2-dihydroquinoline) reagents, the combination of
5 1-ethyl(3,3'-dimethyl-1'-aminopropyl)carbodiimide (EDAC) and HOBt, and the like, as discussed in J. Jones, "Amino Acid and Peptide Synthesis," Steven G. Davis ed., Oxford University Press, Oxford, pp. 25-41 (1992); M. Bodanzky, "Principles of Peptide Synthesis," Hafner et al. ed., Springer-Verlag, Berlin Heidelberg, pp. 9-52 and pp. 202-251 (1984); M. Bodanzky, "Peptide Chemistry, A Practical Textbook," Springer-Verlag, Berlin
10 Heidelberg, pp. 55-73 and pp. 129-180; and Stewart and Young, "Solid Phase Peptide Synthesis," Pierce Chemical Company, (1984), all of which are herein incorporated by reference. The amino protecting group is then removed and the resulting amine is coupled to the (N-substituted) oxamic acid of Formula IX (Step E). Again, this coupling reaction uses the standard peptide coupling reactions mentioned above.

15 The acyl sulfonamide intermediate of Formula XI is reacted in Step G with TBAF in THF overnight to deprotect the alcohol, which may be converted to the corresponding carbonyl of Formula I by employing the Dess-Martin periodinane reagent and DCM at room temperature for 30 minutes.

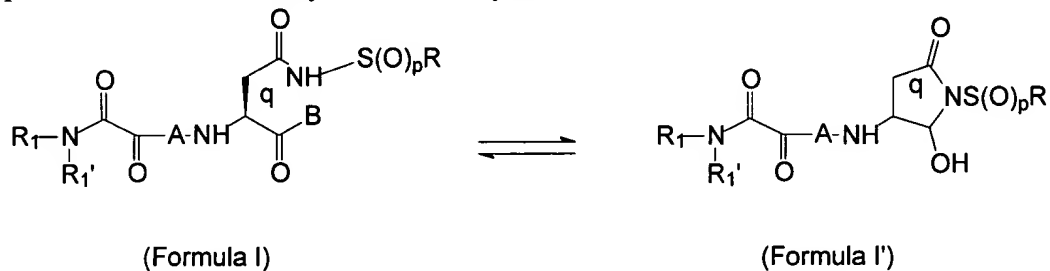
20 Alternatively, a stabilized cyclic acyl sulfonamide may first be formed and then added to the remainder of the molecule via amide bond formation with the carboxy terminus of the natural or unnatural amino acid A, as illustrated in Reaction Scheme 3.

Reaction Scheme 3

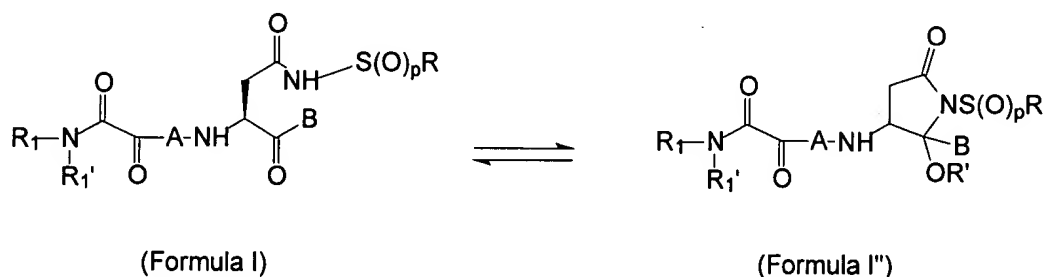


This reaction is further illustrated in Example 5 below.

- Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take a cyclized form, which forms are included in the instant invention. In particular, when B is hydrogen compounds of Formula I may exist in the cyclic Formula I' shown below:



When B is a moiety other than hydrogen, and depending upon the choice of solvents (*e.g.*, R'OH), the compounds of the cyclic form also include compounds having Formula I'' as shown below.



In Formula I'' above, R' includes alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, substituted (1 or 2 naphthyl)alkyl, heterocycle, substituted heterocycle, (heterocycle)alkyl, or substituted (heterocycle)alkyl.

In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present invention.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle (hereinafter collectively referred to as "pharmaceutically-acceptable carriers"). Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchange, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin; buffer substances such as the various phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids; water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts; colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyarylates, waxes,

polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat, and the like.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or by an implanted reservoir. Oral and parenteral administration are preferred. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carrier which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in capsule form useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending

agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared
5 by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible
10 to topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum,
propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and
15 water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to
20 the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-applied transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in
25 saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The compounds of this invention may be used in combination with either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxigenase inhibitors and antagonists of cytokines other than IL-1 β .

The compounds of this invention can also be administered in combination
5 with immunomodulators (*e.g.*, bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexons and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination
10 therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical compositions according to this invention may be comprised of a combination of a compound of Formula I and another therapeutic or prophylactic agent mentioned above.

The disease states which may be treated or prevented by the instant
15 pharmaceutical compositions include, but are not limited to, inflammatory diseases, autoimmune diseases and neurodegenerative diseases, and for inhibiting unwanted apoptosis involved in ischemic injury, such as ischemic injury to the heart (*e.g.*, myocardial infarction), brain (*e.g.*, stroke), and kidney (*e.g.*, ischemic kidney disease). As a consequence of their ability to inhibit apoptosis, the present pharmaceutical compositions
20 are also useful for the repopulation of hematopoietic cells of a patient following chemotherapy. Methods of administering an effective amount of the above-described pharmaceutical compositions to mammals, also referred to herein as patients, in need of such treatment (that is, those suffering from inflammatory diseases, autoimmune diseases, neurodegenerative diseases and for the repopulation of hematopoietic cells in cancer
25 patients who have undergone chemotherapy) are another aspect of the instant invention. Finally, as a further consequence of their ability to inhibit apoptosis, the instant pharmaceutical compositions may be used in a method to prolong the viability of organs to be used in transplantations.

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Inflammatory disease which may be treated or prevented include, for example, septic shock, septicemia, and adult respiratory distress syndrome. Target autoimmune diseases include, for example, rheumatoid, arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, 5 insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis and multiple sclerosis. Target neurodegenerative diseases include, for example, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and primary lateral sclerosis. The pharmaceutical compositions of this invention may also be used to promote wound healing. 10 Target diseases associated with harmful, apoptosis, in other words, those associated with ischemic injury, includes myocardial infarction, stroke, and ischemic kidney disease. The pharmaceutical compositions of this invention may also be used to treat infectious diseases, especially those involved with viral infections.

The term "effective amount" refers to dosage levels of the order of from 15 about 0.05 milligrams to about 140 milligrams per kilogram of body weight per day for use in the treatment of the above-indicated conditions (typically about 2.5 milligrams to about 7 grams per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 milligrams of the compound per kilogram of body weight per day (about 0.5 milligrams to about 3.5 grams per patient per day).

20 The amount of the compounds of Formula I that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 milligrams to 5 grams of a compound of Formula I combined with an appropriate and convenient amount of a pharmaceutically- 25 acceptable carrier which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 milligram to about 500 milligrams of an active compound of Formula I.

It will be understood, however, that the specific "effective amount" for any particular patient will depend upon a variety of factors including the activity of the specific

compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing prevention or therapy.

Although this invention focuses on the use of the compounds disclosed
5 herein for preventing and treating IL-1-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to the ICE/ced-3 family of cysteine protease or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives,
10 may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following
15 examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way. In the following Examples, proton NMR spectra were obtained at 300 MHz; chemical shifts are quoted downfield from internal tetramethylsilane.

20

EXAMPLE 1

ASSAY FOR INHIBITION OF ICE/CED-3 PROTEASE FAMILY ACTIVITY

A. Determination of IC₅₀ Values

Fluorescence enzyme assays detecting the activity of the compounds of Formula I utilizing the recombinant ICE and CPP32 enzymes are performed essentially
25 according to Thornberry et al. (*Nature* 356:768:774 (1992)) and Nicholson et al. (*Nature* 376:37-43 (1995)) respectively, (herein incorporated by reference) in 96 well microtiter plates. The substrate is Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC) for the ICE assay and Acetyl-Asp-Glu-Val-Asp-amino-4-methylcoumarin for the CPP32, Mch2,

Mch3 and Mch5 assays. Enzyme reactions are run in ICE buffer (25 mM HEPES, 1 mM EDTA, 0.1% CHAPS, 10% sucrose, pH 7.5) containing 2 mM DTT at room temperature in duplicate. The assays are performed by mixing the following components:

5 50 μ L ICE, Mch2, Mch5, CPP32 (18.8, 38, 8.1 and 0.153 nM concentrations, respectively) or Mch3 (1 unit) enzyme in ICE buffer containing either 8.0 (ICE, Mch2, Mch3, CPP32) or 20 (Mch5) mM DTT;

50 μ L compound of Formula 1 or ICE buffer (control); and

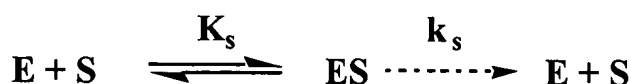
100 μ L of 20 μ M substrate.

10 The enzyme and the compound of Formula I to be assayed are allowed to preincubate in the microtitre plate wells for 30 minutes at room temperature prior to the addition of substrate to initiate the reaction. Fluorescent AMC product formation is monitored for one hour at room temperature by measuring the fluorescence emission at 460 nm using an excitation wavelength of 360 nm. The fluorescence change in duplicate (control) wells are averaged and the mean values are plotted as a function of inhibitor
15 concentration to determine the inhibitor concentration producing 50% inhibition (IC_{50}).

B. Determination of the dissociation constant K_i and irreversible rate constant k_3 for irreversible inhibitors

For the irreversible inhibition of a ICE/ced-3 Family Protease enzyme with a competitive irreversible inhibitor; using the model represented by the following formulas:

20



The product formation at time t may be expressed as:

$$[P]_t = [E]^T \left(\frac{[S]K_i}{[I]K_s} \right) \left(\frac{k_s}{k_3} \right) \left[1 - e^{-k_3 t / (1 + \frac{K_i}{[I]} (1 + \frac{[S]}{K_s}))} \right]$$

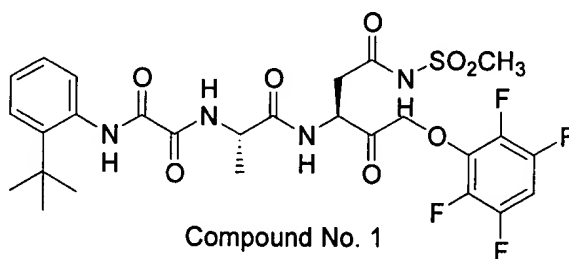
Equation 1

where E, I, EI and E-I denote the active enzyme, inhibitor, non-covalent enzyme-inhibitor complex and covalent enzyme-inhibitor adduct, respectively. The K_i value is the overall dissociation constant of the reversible binding steps, and k_3 is the irreversible rate constant. The $[S]$ and K_s values are the substrate concentration and dissociation constant of the substrate bound to the enzyme, respectively. $[E]^T$ is the total enzyme concentration.

10

EXAMPLE 2

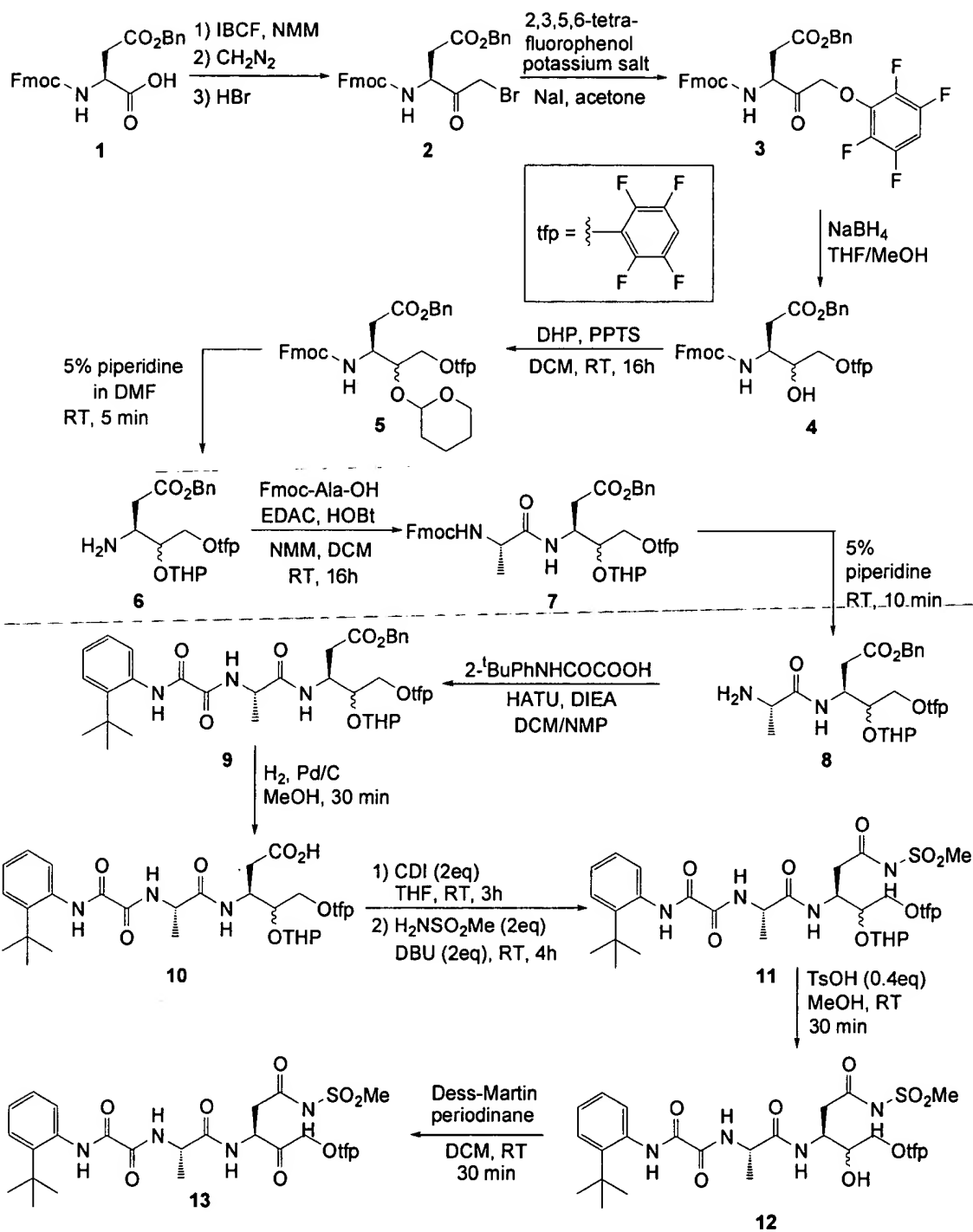
3S)-N -METHANESULFONYL-3-[N-(N'-(2-T-BUTYLPHENYL)OXAMYL)VALINYL] AMINO-5-(2',3',5',6'-TETRAFLUOROPHENOXY)-4-OXAPENTANAMIDE



Compound No. 1

15

Compound No. 1 was made according to the following reaction scheme, the procedures for which are set forth below.



Bromomethylketone 2:

4-Methylmorpholine (0.76 mL, 6.9 mmol) was added to a solution of Fmoc-Asp(OBn)-OH (1) (2.05 g, 4.62 mmol) in 50 mL of dry THF at -10°C under an atmosphere of nitrogen, followed by the addition of isobutyl chloroformate (0.90 mL, 6.9 mmol), and the solution was stirred for 20 minutes. The resulting white precipitate was removed by filtration and the filtrate was cooled to 0°C. In a separate flask, 1-methyl-3-nitro-1-nitrosoguanidine (1.10 g, 7.44 mmol) was added to a vigorously stirred mixture of diethyl ether (14 mL) and 40% KOH (8 mL) at 0°C. The resulting mixture was stirred for 10 minutes and the layers were allowed to separate. The ether layer was transferred via plastic pipette to the mixed anhydride in THF and the reaction mixture was stirred for 30 minutes. Then, 48% HBr in water (2.10 mL) was added and the reaction mixture was warmed to room temperature over 15 minutes. The solution was diluted with ethyl acetate, washed twice with saturated aqueous sodium bicarbonate, once with brine, dried (MgSO₄), and concentrated. The resulting crude product was purified by flash chromatography on silica gel, eluting with 35% ethyl acetate-hexanes, to afford 1.70 g (71%) of 2 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 7.77 (d, J=8 Hz, 2H), 7.58 (d, J=8 Hz, 2H), 7.45-7.29 (m, 9H), 5.77 (d, J=9 Hz, 1H), 5.12 (s, 2H), 4.79-4.71 (m, 1H), 4.63-4.42 (m, 2H), 4.21 (t, J=6 Hz, 1H), 4.04 (s, 2H), 2.97 (ABXq, J=17, 5 Hz, 2H).

Ketone 3:

Sodium iodide (205 mg, 1.37 mmol) was added to a solution of 2 (3.39 g, 6.49 mmol) in 20 mL of acetone at room temperature, followed by the addition of the potassium salt of 2,3,5,6-tetrafluorophenol (1.39 g, 6.82 mmol) and the resulting mixture was stirred for one hour. The reaction mixture was diluted with ethyl acetate, washed twice with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 1:1:3 dichloromethane/diethyl ether/hexanes, to provide 3.32 g (84%) of 3 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 7.76 (d, J=8 Hz, 2H), 7.58 (d, J=8 Hz, 2H), 7.44-7.27 (m, 9H), 6.85-6.73 (m, 1H), 5.73 (d, J=9 Hz, 1H),

5.15-4.92 (m, 4H), 4.75-4.67 (m, 1H), 4.61-4.42 (m, 2H), 4.21 (t, J=6 Hz, 1H), 3.00 (ABXq, J=18, 4 Hz, 2H).

Alcohol 4:

Sodium borohydride (248 mg, 6.56 mmol) was added to a solution of 3 (608 mg, 5.43 mmol) in 14 mL of dry methanol and 14 mL of dry THF at 0 °C and the resulting mixture was stirred for 30 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution, extracted three times with dichloromethane, and the combined dichloromethane layers were washed once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate-hexanes, to give 2.43 g (73%) of 4 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 7.78-7.74 (m, 2H), 7.57 (d, J=7 Hz, 2H), 7.44-7.27 (m, 9H), 6.87-6.75 (m, 1H), 5.62 (d, J=9 Hz, 0.3H), 5.44 (d, J=9 Hz, 0.2H), 5.29-5.23 (m, 0.5H), 5.16-5.11 (m, 1H), 4.69 (d, J=6 Hz, 1H), 4.59-4.37 (m, 4H), 4.30-4.04 (m, 3H), 3.35-3.09 (m, 1H), 2.94-2.41 (m, 2H).

THP Ether 5:

3,4-Dihydro-2H-pyran (0.55 mL, 6.0 mmol) and pyridinium p-toluenesulfonate (218 mg, 0.866 mmol) were added to a solution of 4 (2.43 g, 3.99 mmol) in 20 mL of dry dichloromethane and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed twice with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, first eluting with 15% ethyl acetate-hexanes and then with 50% ethyl acetate-hexanes, to afford 1.71 g (62%) of 5 as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.76 (d, J=7 Hz, 2H), 7.62-7.55 (m, 2H), 7.42-7.27 (m, 9H), 6.84-6.71 (m, 1H), 6.21 (d, J=9 Hz, 0.3H), 5.65 (d, J=9 Hz, 0.2H), 5.33-5.27 (m, 0.5H), 5.13 (t, J=3 Hz, 2H), 4.72-4.04 (m, 8H), 3.91-3.73 (m, 1H), 3.51-3.36 (m, 1H), 2.98-2.57 (m, 2H), 1.86-1.61 (m, 2H), 1.57-1.43 (m, 4H).

Amine 6:

Piperidine (0.75 mL, 7.6 mmol) was added to a solution of 5 (1.70 g, 2.45 mmol) in 15 mL of dry DMF at room temperature and the resulting solution was stirred for 5 minutes. The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, twice with water, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, first eluting with 50% ethyl acetate-hexanes and then with 80% ethyl acetate-hexanes, to provide 793 mg (69%) of 6 as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 7.39-7.29 (m, 5H), 6.82-6.70 (m, 1H), 5.15 (s, 2H), 4.78-4.63 (m, 1H), 4.53-4.26 (m, 2H), 4.03-3.79 (m, 2H), 3.71-3.43 (m, 2H), 2.80-2.43 (m, 2H), 1.85-1.66 (m, 2H), 1.57-1.45 (m, 4H).

Dipeptide 7:

Amine 6 (790 mg, 1.68 mmol) and Fmoc-Ala-OH (578 mg, 1.86 mmol) were dissolved in 40 mL of dry dichloromethane. 1-Hydroxybenzotriazole hydrate (342 mg, 2.53 mmol) was added to this solution, followed by the addition of 4-methylmorpholine (0.30 mL, 2.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (391 mg, 2.04 mmol), and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, once with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with 40% ethyl acetate-hexanes, to give 1.17 g (91%) of 7 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 7.76 (d, J=7 Hz, 2H), 7.62-7.55 (m, 2H), 7.40 (t, J=7 Hz, 2H), 7.35-7.28 (m, 7H), 6.95-6.46 (m, 2H), 5.45-5.25 (m, 1H), 5.11-5.05 (m, 2H), 4.75-4.30 (m, 5H), 4.28-4.04 (m, 4H), 3.94-3.76 (m, 1H), 3.50-3.36 (m, 1H), 2.95-2.61 (m, 2H), 1.82-1.65 (m, 2H), 1.54-1.41 (m, 4H), 1.39-1.32 (m, 3H).

Amine 8:

Piperidine (0.50 mL, 5.1 mmol) was added to a solution of 7 (1.17 g, 1.53 mmol) in 10 mL of dry DMF at room temperature and the resulting solution was stirred for 10 minutes. The reaction mixture was diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, twice with water, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography on silica gel, first eluting with 50% ethyl acetate-hexanes and then with 20% methanol-dichloromethane, to provide 806 mg (97%) of 8 as a yellow oil. ¹H-NMR (300 MHz, CDCl₃): δ 8.01 (d, J=9 Hz, 0.35H), 7.93 (d, J=9 Hz, 0.24H), 7.64 (d, J=9 Hz, 0.17H), 7.56 (d, J=9 Hz, 0.24H), 7.38-7.28 (m, 5H), 6.83-6.70 (m, 1H), 5.17-5.06 (m, 2H), 4.76-4.24 (m, 4H), 4.23-4.03 (m, 1H), 3.91-3.79 (m, 1H), 3.51-3.38 (m, 2H), 2.95-2.61 (m, 2H), 1.85-1.66 (m, 2H), 1.59-1.41 (m, 4H), 1.29-1.25 (m, 3H).

Oxamide 9:

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

hexafluorophosphate (308 mg, 0.809 mmol) was added to 2-t-butylphenyloxamic acid (150 mg, 0.678 mmol) in 0.75 mL of dry NMP and 1.5 mL of dry dichloromethane at room temperature. The mixture was stirred for 15 minutes, and then a solution of 8 (365 mg, 0.672 mmol) in 1.5 mL of dry dichloromethane was added, followed by the addition of diisopropylethyl amine (0.35 mL, 2.0 mmol). The reaction mixture was stirred for 14 hours, diluted with ethyl acetate, washed once with saturated aqueous ammonium chloride solution, once with saturated aqueous sodium bicarbonate solution, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography, eluting with 35% ethyl acetate-hexanes, to give 315 mg (63%) of 9 as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 9.57 (s, 0.4H), 9.54 (s, 0.6H), 8.11-7.95 (m, 2H), 7.44-7.24 (m, 7H), 7.21-7.13 (m, 1H), 6.96-6.50 (m, 2H), 5.13-5.07 (m, 2H), 4.77-4.05 (m, 6H), 3.97-3.77 (m, 1H), 3.55-3.39 (m, 1H), 2.96-2.62 (m, 2H), 1.85-1.61 (m, 2H), 1.55-1.37 (m, 16H).

Acid 10:

10% Palladium on carbon (76 mg) was added to a solution of 9 (300 mg, 0.402 mmol) in anhydrous methanol (7 mL) under an atmosphere of nitrogen and the flask was then evacuated with the house vacuum. The mixture was stirred under a balloon of hydrogen gas for 30 minutes, then filtered through Celite, and eluted with methanol. The solution was concentrated to afford 249 mg (94%) of 10 as a white solid.

Methyl sulfonamide 11:

1,1'-Carbonyldiimidazole (124 mg, 0.766 mmol) was added to a solution of 10 (249 mg, 0.380 mmol) in dry THF (6 mL) under an atmosphere of nitrogen, and the reaction mixture was stirred for 3 hours. The mixture was cooled to 0°C, and the methanesulfonamide (73 mg, 0.77 mmol) was added, followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.115 mL, 0.77 mmol). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate, washed once with 1 N HCl solution, twice with water, once with brine, dried (MgSO₄), and concentrated. The residue was reconcentrated from dichloromethane to provide 271 mg (97%) of 11 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 9.59-9.48 (m, 1H), 8.25-8.15 (m, 1H), 7.95-7.88 (m, 1H), 7.69 (d, J=8 Hz, 0.3H), 7.44-7.38 (m, 1H), 7.28-7.13 (m, 2.4H), 6.93-6.87 (m, 0.3H), 6.85-6.71 (m, 1H), 4.75-4.33 (m, 4H), 4.27-4.01 (m, 3H), 3.87-3.43 (m, 1H), 3.28-3.23 (m, 3H), 2.93-2.56 (m, 2H), 1.86-1.68 (m, 2H), 1.55-1.39 (m, 16H).

Alcohol 12:

p-Toluenesulfonic acid (21 mg, 0.11 mmol) was added to a solution of 11 (202 mg, 0.275 mmol) in anhydrous methanol (3 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate, washed three times with water, once with brine, dried (MgSO₄), and concentrated to afford 166 mg (93%) of 12 as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 9.57-9.46 (m, 1H), 8.34 (t, J=8 Hz, 1H), 7.80 (d, J=8 Hz, 1H), 7.44-7.30 (m, 2H), 7.23-7.12 (m, 2H), 6.83-6.69 (m,

1H), 4.66-4.45 (m, 3H), 4.33-4.10 (m, 3H), 3.26 (s, 1.2H), 3.25 (s, 1.8H), 2.90-2.76 (m, 2H), 1.48-1.38 (m, 12H).

Methylsulfonamide 13 ("Compound No. 1"):

Dess-Martin periodinane (126 mg, 0.297 mmol) was added to a solution of 12 (154 mg, 0.238 mmol) in 5 mL of dry dichloromethane, and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate, washed twice with water, once with brine, dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography, eluting first with 60% ethyl acetate-hexanes and then with 80% ethyl acetate-hexanes, to provide 114 mg (74%) of 13 as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ 9.53 (s, 1H), 8.27-7.87 (m, 2H), 7.42 (d, *J*=8 Hz, 1H), 7.29-7.15 (m, 2H), 6.92-6.77 (m, 2H), 5.02-4.77 (m, 3H), 4.56-4.27 (m, 2H), 3.37 (s, 3H), 3.06-2.60 (m, 2H), 1.56-1.42 (m, 12H); MS (ESI) *m/e* 645 [(M⁺) -1].

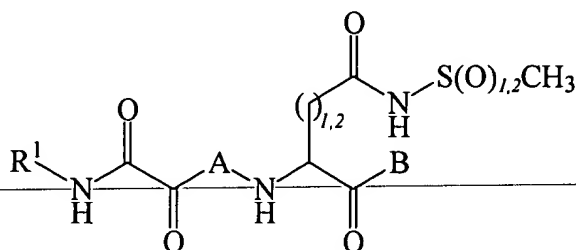
EXAMPLE 3

REPRESENTATIVE COMPOUNDS

The representative compounds listed in the following Table 1 may be made according to the procedures set forth in Example 2.

Table 1

Representative Compounds



Cpd	A	B	R ¹
1	NHCH(CH ₂ CH(CH ₃) ₂)CO	H	1-naphthyl
2	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ F	1-naphthyl
3	NHCH(CH(CH ₃) ₂)CO	CH ₂ F	1-naphthyl
4	NHCH(CH(CH ₃) ₂)CO	CH ₂ OCO(2,4-diCl-Ph)	1-naphthyl
5	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,6-diF-Ph)	1-naphthyl
6	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,4,6-triF-Ph)	1-naphthyl
7	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-naphthyl
8	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(6-Me-2-pyron-4-yl)	1-naphthyl
9	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2-Ph-5,6-benzopyran-4-on-3-yl)	1-naphthyl
10	NHCH(CH(CH ₃) ₂)CO	CH ₂ OPO(Me)Ph	1-naphthyl
11	NHCH(CH(CH ₃) ₂)CO	CH ₂ OPOPh ₂	1-naphthyl
12	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2-CF ₃ -pyrimidin-4-yl)	1-naphthyl
13	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(5-CO ₂ Me-isoxazol-3-yl)	1-naphthyl
14	NHCH(CH(CH ₃) ₂)CO	CH ₂ OPO(Me)(1-naphthyl)	1-naphthyl
15	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ OPOPh ₂	1-naphthyl

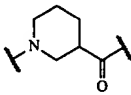
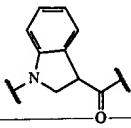
Cpd	A	B	R ¹
16	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ OCO(2,6-diCl-Ph)	1-naphthyl
17	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ O(2,4,6-triF-Ph)	1-naphthyl
18	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-naphthyl
19	NHCH(CH ₂ CH(CH ₃) ₂)CO	CH ₂ OPO(Me)Ph	1-naphthyl
20	NHCH(CH ₃)CO	CH ₂ O(2-F-Ph)	(2-Ph)Ph
21	NHCH(CH ₃)CO	CH ₂ OCO(2,6-di-Cl-Ph)	(2-Ph)Ph
22	NHCH(CH ₃)CO	CH ₂ OPOPh ₂	(2-Ph)Ph
23	NHCH(CH ₃)CO	CH ₂ O(2-F-Ph)	(2-t-Bu)Ph
24	NHCH(CH ₃)CO	CH ₂ OPOPh ₂	(2-t-Bu)Ph
25	NHCH(CH ₃)CO	CH ₂ OCO(2,3,5,6-tetra-Cl-Ph)	1-naphthyl-CH ₂
26	NHCH(CH ₃)CO	CH ₂ OCO(2,6-di-Cl-Ph)	1-naphthyl-CH ₂
27	NHCH(CH ₃)CO	CH ₂ OPOPh ₂	1-naphthyl-CH ₂
28	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-naphthyl-CH ₂
29	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	PhCH ₂
30	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph(CH ₂) ₂
31	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph ₂ CH

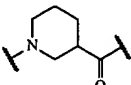
Cpd	A	B	R ¹
32	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph
33	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-Ph)Ph
34	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhCH ₂)Ph
35	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(3-PhO)Ph
36	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	4-Cl-1-naphthyl
37	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2-anthryl
38	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2-benzimidazolyl
39	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-adamantanyl
40	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-F)Ph
41	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(4-F)Ph
42	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-CF ₃)Ph
43	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-t-Bu)Ph
44	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(4-n-heptyl)Ph
45	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-CH ₃ O)Ph
46	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
47	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2-naphthyl

Cpd	A	B	R ¹
48	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	5,6,7,8-tetrahydro-1-naphthyl
49	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-anthryl
50	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2-pyridinyl
51	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	4-pyridinyl
52	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2,3,5,6-tetrafluoro-4-pyridinyl
53	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	2-pyrazinyl
54	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1,2,3,4-tetrahydro-1-naphthyl
55	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-Cl)Ph
56	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-Br)Ph
57	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-I)Ph
58	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,6-di-F)Ph
59	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,5-di-t-Bu)Ph
60	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	5-indanyl

Cpd	A	B	R ¹
61	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(3,4,5-tri-MeO)PhCH ₂
62	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	methyl
63	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	n-heptyl
64	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	t-octyl
65	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	cyclo-hexyl
66	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	5-Ph-3-pyrazolyl
67	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-F-4-I)Ph
68	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,3,4,5-tetra-F)Ph
69	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,3,4,6-tetra-F)Ph
70	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,3,5,6-tetra-Cl)Ph
71	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,3,4,5,6-penta-F)Ph
72	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph ₂ N
73	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	PHCH ₂ (Ph)N
74	NHCH(CH(CH ₃) ₂)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	PhCH ₂ O
75	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-t-Bu)Ph

Cpd	A	B	R ¹
76	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-CF ₃)Ph
77	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-Ph)Ph
78	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhCH ₂)Ph
79	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
80	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(3-PhO)Ph
81	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	5,6,7,8-tetrahydro-1-naphthyl
82	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-naphthyl
83	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph
84	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2,6-di-F)Ph
85	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(4-Ph)Ph
86	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(4-MeO)Ph
87	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	Ph ₂ CH
88	NHCH(CH ₂ cyclohexyl)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhO)Ph
89	NHCH(CH ₂ cyclohexyl)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-Ph)Ph
90	NHCH(CH ₂ cyclohexyl)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-PhCH ₂)Ph
91	NHCH(CH ₂ cyclohexyl)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	1-naphthyl

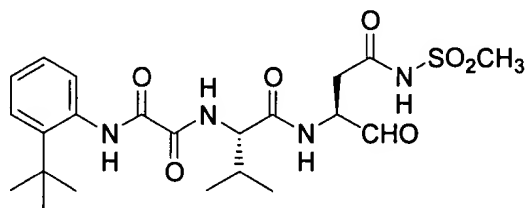
Cpd	A	B	R ¹
92	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OCO(2,6-diCl-Ph)	5,6,7,8-tetrahydro-1-naphthyl
93	NHCH(CH ₂ cyclohexyl)CO	CH ₂ O(2,3,5,6-tetra-F-Ph)	5,6,7,8-tetrahydro-1-naphthyl
94	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPO(Me)Ph	5,6,7,8-tetrahydro-1-naphthyl
95	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPOPh ₂	5,6,7,8-tetrahydro-1-naphthyl
96	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPO(Me)Ph	(2-PhCH ₂)Ph
97	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPOPh ₂	(2-PhCH ₂)Ph
98	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPO(Me)Ph	(2-Ph)Ph
99	NHCH(CH ₂ cyclohexyl)CO	CH ₂ OPOPh ₂	(2-Ph)Ph
100		CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
101		CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
102	NHCH(cyclohexyl)CO	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl

Cpd	A	B	R ¹
103	norleucine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
104	(t-butyl)glycine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
105	(t-butyl)alanine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
106	phenylglycine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
107	phenylalanine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
108	homophenylalanine	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
109	1-aminocyclopentane carboxylic acid	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
110	NHCH(CH ₂ CH ₂ SOCH ₃)CO	CH ₂ O(2,3,5,6-tetra-F-Ph)	1-naphthyl
111		H	1-naphthyl
112	NHCH(CH(CH ₃) ₂)CO	H	2-(1H-tetrazol-5-yl)Ph
113	NHCH(CH(CH ₃) ₂)CO	H	1-adamantanyl
114	NHCH(CH(CH ₃) ₂)CO	H	Ph
115	NHCH(CH(CH ₃) ₂)CO	H	PhCH ₂
116	NHCH(CH(CH ₃) ₂)CO	H	Ph(CH ₂) ₂
117	NHCH(CH(CH ₃) ₂)CO	H	(2-CF ₃)Ph
118	NHCH(CH(CH ₃) ₂)CO	H	(2-t-Bu)Ph

Cpd	A	B	R ¹
119	NHCH(CH(CH ₃) ₂)CO	H	(2-Ph)Ph
120	NHCH(CH(CH ₃) ₂)CO	H	(2-PhCH ₂)Ph
121	NHCH(CH(CH ₃) ₂)CO	H	(2-PhO)Ph
122	NHCH(CH(CH ₃) ₂)CO	H	2-naphthyl
123	NHCH(CH(CH ₃) ₂)CO	H	1-naphthyl
124	NHCH(CH(CH ₃) ₂)CO	H	4-Cl-1-naphthyl
125	NHCH(CH(CH ₃) ₂)CO	H	5,6,7,8-tetrahydro-1-naphthyl
126	NHCH(CH(CH ₃) ₂)CO	H	1,2,3,4-tetrahydro-1-naphthyl
127	NHCH(CH(CH ₃) ₂)CO	H	(1-naphthyl)CH ₂
128	NHCH(CH(CH ₃) ₂)CO	H	2-Br-Ph
129	NHCH(CH(CH ₃) ₂)CO	H	2-tBu-Ph
130	NHCH(CH ₃)CO	H	2-Br-Ph
131	NHCH(CH ₃)CO	H	2-tBu-Ph
132	NHCH(CH ₃)CO	H	CH ₂ Ph
133	NHCH(CH ₃)CO	H	(2-PhCH ₂)Ph

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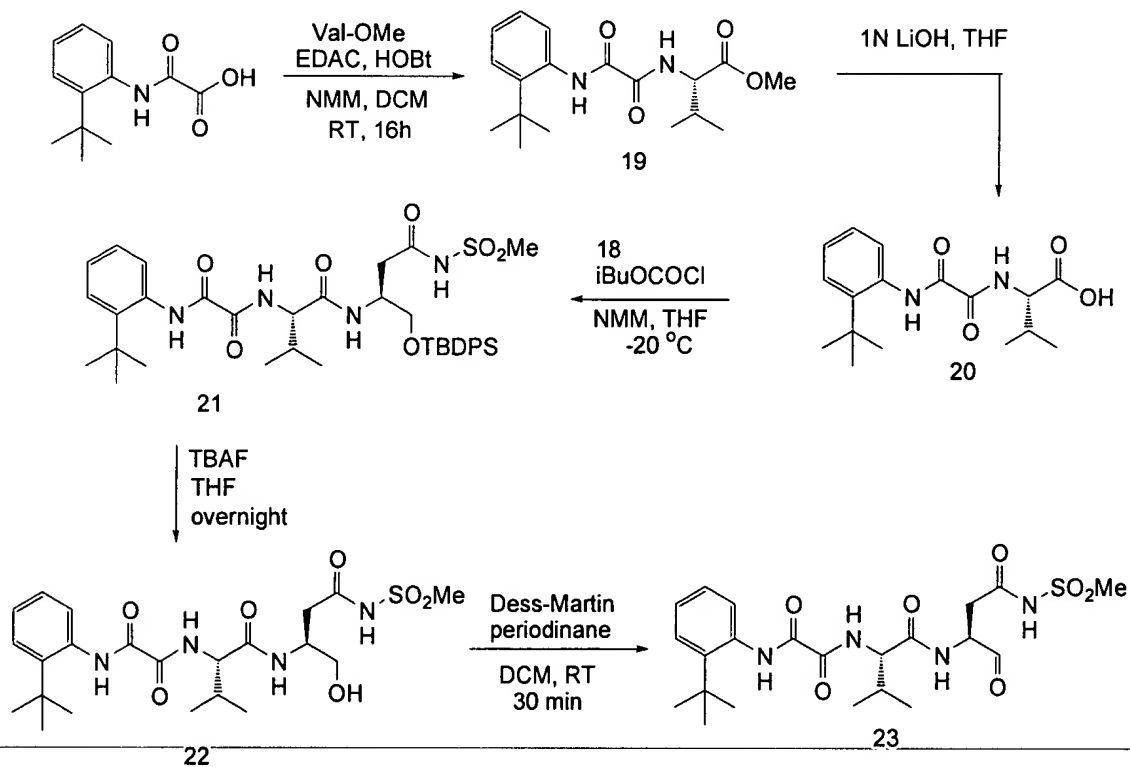
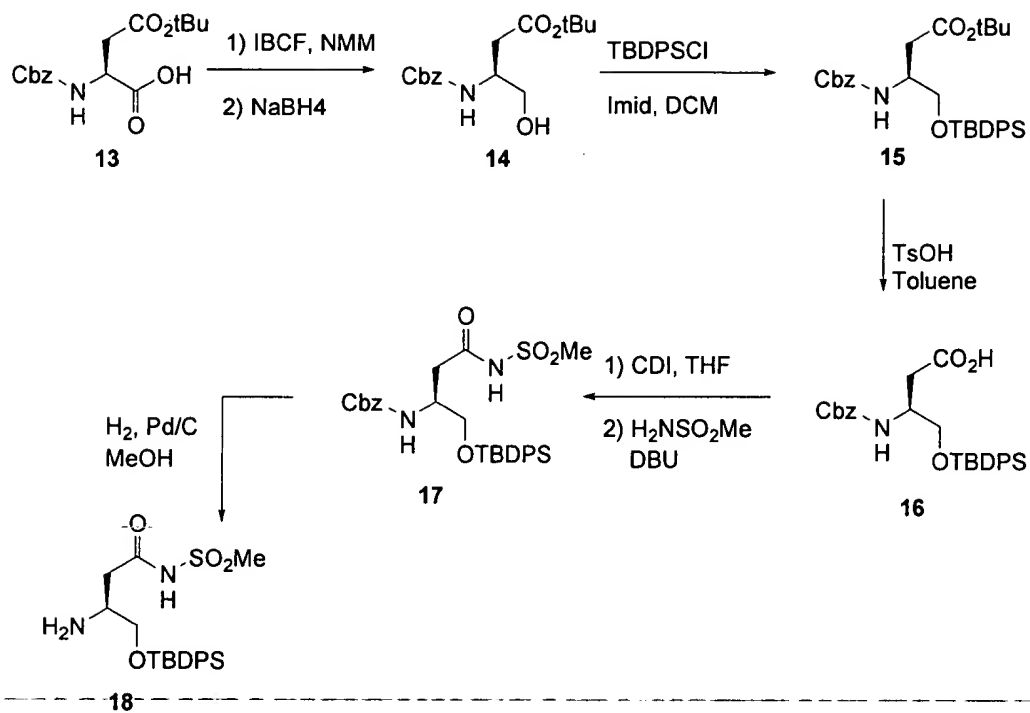
PROPYLCARBAMOYL)-2-METHYL-PROPYL]-OXALAMIDE



Compound No. 118

5

Compound No. 118 was made according to the following reaction scheme, the procedures for which are set forth below.



Alcohol 14:

4-Methylmorpholine (0.78 mL, 7.10 mmol) was added to a solution of Z-Asp(OtBu)-OH (1) (2.4 g, 7.03 mmol) in 50 mL of dry THF at 0 °C under an atmosphere of nitrogen, followed by the addition of isobutyl chloroformate (0.92 mL, 7.10 mmol); the solution was stirred for 10 min. The resulting solution was added to a suspension of sodium borohydride (529.2 mg, 13.99 mmol) in 50 mL of THF and 12 mL of MeOH at -78 °C. After 2 h at -78 °C, the mixture was quenched with 3 mL of acetic acid and diluted with 1:1 ethyl acetate:hexane, washed with diluted NaHCO₃ (2x), dried, and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 2%-10% MeOH-CH₂Cl₂, to afford 2 g (87%) of 14 as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.7-7.9 (m, 5 H), 5.5 (d, J=8.1 Hz, 1 H), 5.1 (s, 2 H), 3.98-4.04 (m, 4.04, 1 H), 3.65-3.75 (m, 2 H), 2.42-2.58 (m, 3 H), 1.43 (s, 9 H).

TBDPS Ether 15:

TBDPS-Cl (0.81 mL, 3.10 mmol) and imidazole (403 mg, 5.92 mmol) was added to a solution of 14 in 2 mL of dichloromethane and the resulting solution was stirred at room temperature for 20 min. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄), and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 10-30% ethyl acetate-hexane, to give 1.45 g of 15 as a colorless oil (94%). ¹H NMR (300 MHz, CDCl₃): δ 7.70-7.73 (m, 4 H), 7.59-7.64 (m, 11 H), 5.28 (d, J = 9 Hz), 5.08 (s, 2 H), 4.08-4.16 (m, 1 H), 3.69-3.71 (m, 1 H), 2.60 (d, 4.2 Hz, 2 H), 1.40 (s, 9 H), 1.05 (s, 9 H).

Acid 16:

p-Toluenesulfonic acid monohydrate (148.35 mg, 0.78 mmol) was added to a solution of 15 (715 mg, 1.3 mmol) in 5 mL of toluene. The resulting mixture was refluxed for 30 min. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL), washed with water (2x10 mL) and brine (10 mL), and concentrated to give almost pure product 16 (626.36 mg, 98%). ¹H NMR (300 MHz, CDCl₃): δ 7.59-7.77 (m,

4 H), 7.30-7.45 (m, 11 H), 5.29-5.34 (m, 1 H), 5.08 (s, 2 H), 4.05-4.17 (m, 1 H), 3.73 (broad s, 2 H), 2.71 (d, J = 6 Hz, 2 H), 1.05 (s, 9 H).

Sulfonamide 17:

1,1'-Carbonyldiimidazole (1.38 g, 8.48 mmol) was added to a solution of 16 (2.07 g, 4.22 mmol) in dry THF (50 mL) under an atmosphere of nitrogen, and the reaction mixture was stirred for 3 h at room temperature. The mixture was cooled to 0 °C, and the methanesulfonamide (807 mg, 8.48 mmol) was added followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.28 g, 8.40 mmol). The resulting mixture was stirred at room temperature for 3 h, diluted with ethyl acetate, washed with 1N HCl, water, brine, dried, and concentrated to give 2.16 g (90%) of 17 as a colorless oil. ¹HNMR (300 MHz, CDCl₃): δ 7.52-7.64 (m, 4 H), 7.30-7.45 (m, 11 H), 5.30-5.35 (m, 1 H), 5.00-5.09 (m, 2 H), 4.02-4.12 (m, 1 H), 3.72 (d, J = 4.5 Hz, 2 H), 3.14 (s, 3 H), 2.60-2.67 (m, 2 H), 1.06 (s, 9 H).

Amine 18:

10% Palladium on carbon was added to a solution of 17 (223 mg, 0.39 mmol) in methanol (10 mL) under an atmosphere of nitrogen and the flask was then evacuated with the house vacuum. The mixture was stirred under a balloon of hydrogen gas for 40 min, then filtered through Celite and eluted with methanol. The solution was concentrated to give 133.12 mg (95%) of 18 as a colorless oil.

Oxamylpeptide 19:

H-Val-OmeHCl (5 g, 29.84 mmol) and 2-tBu-phenyloxamic acid (6.53 g, 29.54 mmol) was dissolved in 50 mL of dry dichloromethane. 1-Hydroxybenzotriazole hydrate (4.39 g, 32.49 mmol) was added to this solution, followed by the addition of 4-methylmorpholine (8.15 mL, 73.85 mmol) and 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.63 g, 50.22 mmol), and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate,

washed with 10% KHSO₄, saturated aqueous sodium bicarbonate solution, and brine. The resulting organic phase was dried and purified to afford 7 g (71%) of 19 as a pale solid. ¹HNMR (300 MHz, CDCl₃): δ 9.58 (s, 1 H), 7.97-8.06 (m, 2 H), 7.42 (dd, J=1.5, 7.8 Hz, 1 H), 7.14-7.31(m, 3 H), 4.54 (dd, J= 5.4, 9.6 Hz, 1 H), 3.80 (s, 3 H), 2.26-2.32 (m, 1 H), 1.46 (s, 9 H), 0.98-1.02 (m, 6 H).

Acid 20:

The dipeptide 7 (1 g, 2.99 mmol) was dissolved in THF (4 mL) followed by the addition of LiOH (1N, 3 mL). The resulting mixture was stirred at 0 °C for 1h. The reaction mixture was quenched with 3 mL of 1N HCl, extracted with ethyl acetate, dried, and concentrated to afford 0.91 g (95%) of acid 20 as a pale solid. ¹HNMR (300 MHz, CDCl₃): δ 9.58 (s, 1 H), 7.9-8.03 (m, 2 H), 7.43 (dd, J=1.8, 8.1Hz, 1 H), 7.15-7.31 (m, 2 H), 4.59 (dd, J=5.1, 9.3 Hz, 1 H), 2.34-2.40 (m, 1 H), 1.46 (s, 9 H), 1.03-1.07 (m, 6 H).

Oxamide 21:

N-methylmorpholine (40μl, 0.36 mmol) was added to a solution of the acid 20 in 2 mL of THF followed by addition of isobutylchloroformate (47 μl, 0.37 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 20 min, and then the amine 18 was added. The resulting mixture was stirred at -20 °C for 3 h, quenched with 1 mL of hydrochloric acid (1N), extracted with ethyl acetate, and washed with water. Drying and concentration gave 220mg (92%) of 21 as a colorless oil. ¹HNMR (300 MHz, DMSO): δ 10.03 (s, 1 H), 8.41(d, J =7.5 Hz, 1 H), 8.33 (d, J = 7.8 Hz, 1 H), 7.21-7.63 (m, 14), 4.24-4.31 (m, 2 H), 4.00-4.10 (m, 1 H), 3.54-3.62 (m, 2 H), 3.15 (s, 3 H), 2.69 (dd, J=6.0, 16.2, 1 H), 2.58 (dd, J=8.4, 16.2, 1 H), 2.01-2.11(m, 1 H), 1.31 (s, 9 H), 0.99 (s, 9 H), 0.80-0.93 (m, 6 H).

Alcohol 22:

TBAF (3 mL, 3.00 mmol) was added to a solution of 21 (200 mg, 0.3 mmol) in THF (3 mL). The reaction mixture was stirred overnight, diluted with ethyl

acetate, washed with water, dried, concentrated, and purified by flash chromatography, eluting with 5-20% MeOH-CH₂Cl₂ to afford 135 mg (90%) of 22 as a white solid.

¹HNMR(300 MHz, CD₃OD): δ 7.64-7.69 (m, 1 H), 7.46-7.50 (m, 1 H), 7.20-7.26 (m, 2 H), 4.25-4.35 (m, 2 H), 3.53-3.66 (m, 2 H), 3.22-3.26 (m, 1 H), 2.63 (dd, J=5.4, 15.3, 1 H),

5 2.49 (dd, J=7.8, 15.3), 2.10-2.20 (m, 1 H), 1.42 (s, 9 H), 0.96-1.02 (m, 6 H).

Aldehyde 23 ("Compound No. 118"):

Dess-Martin periodinane (105 mg, 0.25 mmol) was added to a solution of 22 (90 mg, 0.18 mmol) in 1.5 mL of dichloromethane, and the mixture was stirred at room temperature for 30 min. The mixture was diluted with ethyl acetate, washed with
10 water, dried, and concentrated. The crude product was purified by preparative TLC (7% MeOH-CH₂Cl₂) to give 58 (65%) mg of 23 as a foam. ¹HNMR (300 MHz, CD₃OD): δ 7.64-8.19 (m, 3 H), 7.45-7.49 (m, 1 H), 7.17-7.29 (m, 2 H), 4.55-4.75 (m, 1 H), 4.24-4.36 (m, 2 H), 3.01 (s, 3 H), 2.33-2.78 (m, 2 H), 2.00-2.1 (m, 1 H), 1.28-1.42 (s, 9 H), 0.91-1.02 (m, 6 H).

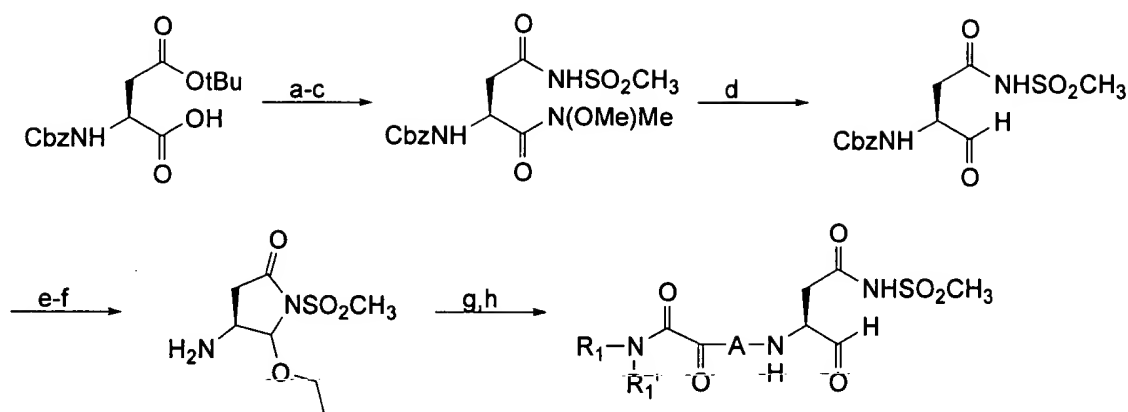
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EXAMPLE 5

ALTERNATIVE SYNTHESIS OF COMPOUNDS OF FORMULA I

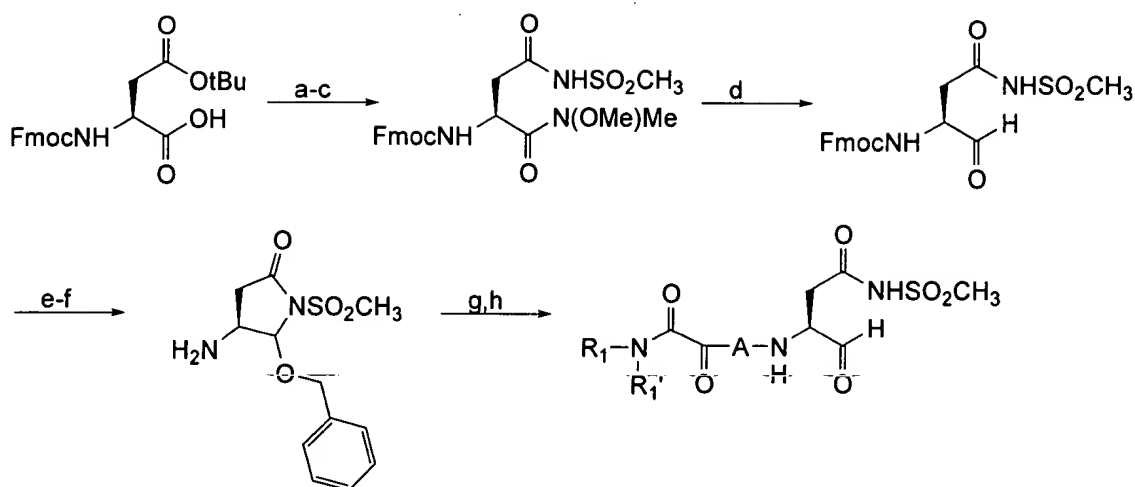
This example illustrates synthesis of compounds of Formula I by formation
20 of a stabilized sulfonamide ring, followed by addition via amide bond formation to the remainder of the compound. In the following representative examples, *q* is 1, *p* is 2 and R is methyl.

Scheme 3a



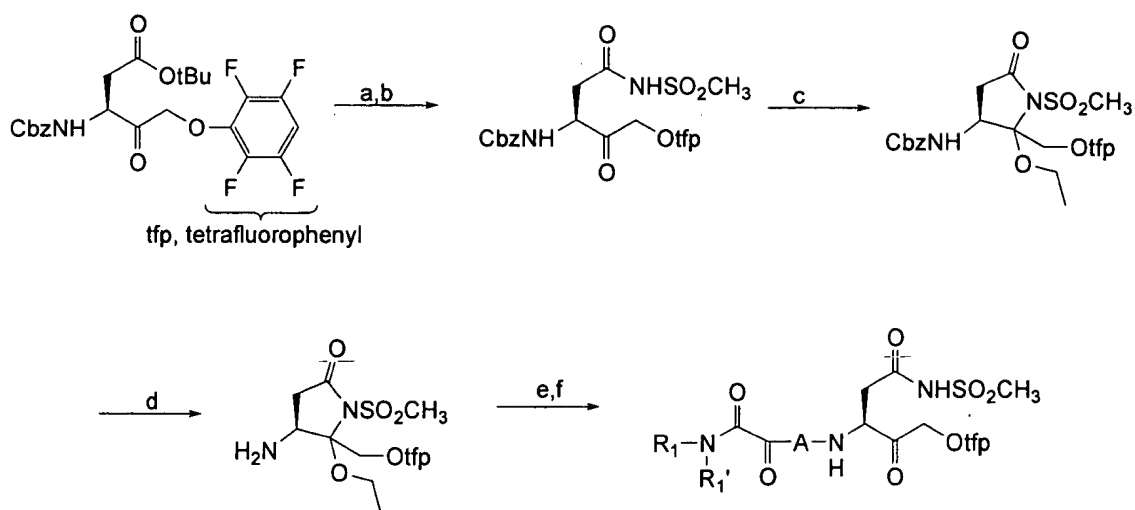
- Starting with the commercially available Z-Asp(OtBu)-OH, the Weinreb amide is formed, followed by hydrolysis of the t-butyl ester. The beta carboxylic acid is then coupled with methyl sulfonamide (or other substituted sulfonamide), followed by reduction of the Weinreb amide to the aldehyde. Acid-catalyzed acetal formation using ethanol is assisted by cyclization of the sulfonamide to form a stable 5-membered ring. The carbobenzyloxy urethane is then removed, the aspartyl intermediate coupled to the substituted oxamyl peptide of choice, then the acetal deprotected. (a) EDCI, HOBT, N-Me Morpholine, CHCl₂, 0°C-RT; (b) TFA, anisole, CH₂Cl₂, RT; (c) EDCI, DMAP (cat.), CH₃SO₂NH₂, CH₂Cl₂, RT; or i. CDI; ii. CH₃SO₂NH₂, DBU, 0°C, (d) LAH, THF, 0°C; (e) Ethanol, CH(OEt)₃, p-TsOH, toluene reflux; (f) H₂; Pd/C, RT; (g) R₁(R₁')NCOCONH(amino acid)CO₂H, EDCI, HOBT, N-Me Morpholine, CH₂Cl₂, 0°C-RT; (h) TFA, anisole, CH₂Cl₂, H₂O RT.

Scheme 3b



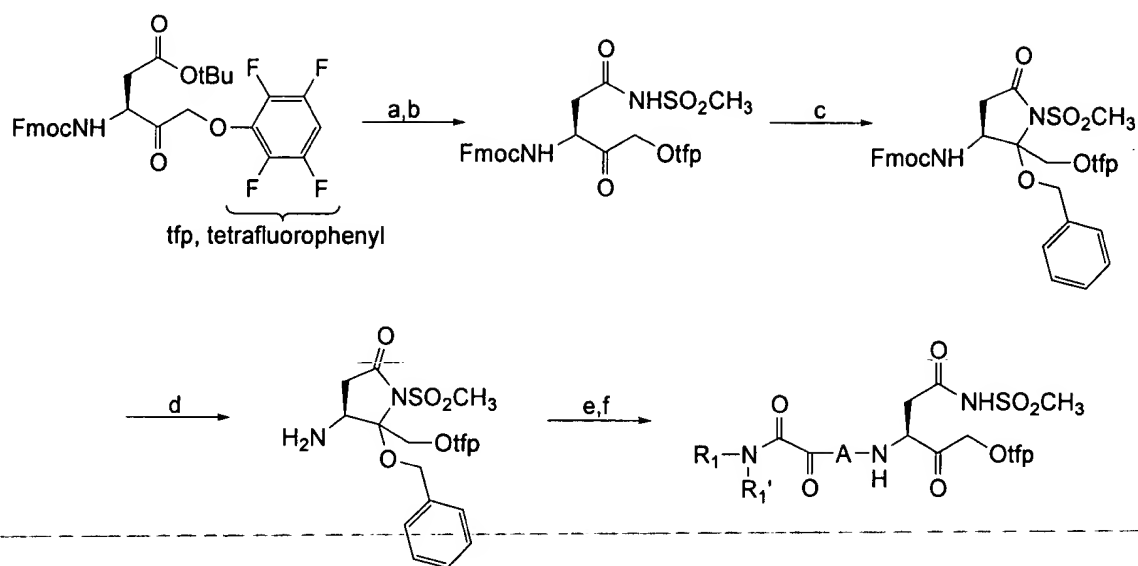
- Starting with the commercially available Fmoc-Asp(OtBu)-OH, the Weinreb
- 5 amide is formed, followed by hydrolysis of the t-butyl ester. The beta carboxylic acid is then coupled with methyl sulfonamide (or other substituted sulfonamide), followed by reduction of the Weinreb amide to the aldehyde. Acid-catalyzed acetal formation using benzyl alcohol is assisted by cyclization of the sulfonamide to form a stable 5-membered ring. The fluorenylmethoxy urethane is then removed, the aspartyl intermediate coupled
 - 10 to the substituted oxamyl peptide of choice, then the acetal deprotected. (a) EDCI, HOBT, N-Me Morpholine, HClH₂N(OCH₃)CH₃, CH₂Cl₂, 0°C-RT; (b) TFA, anisole, CH₂Cl₂, RT; (c) EDCI, DMAP (cat.), CH₃SO₂NH₂, CH₂Cl₂, RT; (d) LAH, THF, 0°C; (e) Benzyl alcohol, p-TsOH, toluene reflux; (f) Et₂NH, DMF, RT; (g) R₁(R₁')NCOCO₂H, EDCI, HOBT, N-Me Morpholine, CH₂Cl₂, 0°C-RT; (h) H₂; Pd/C, RT.

Scheme 3c



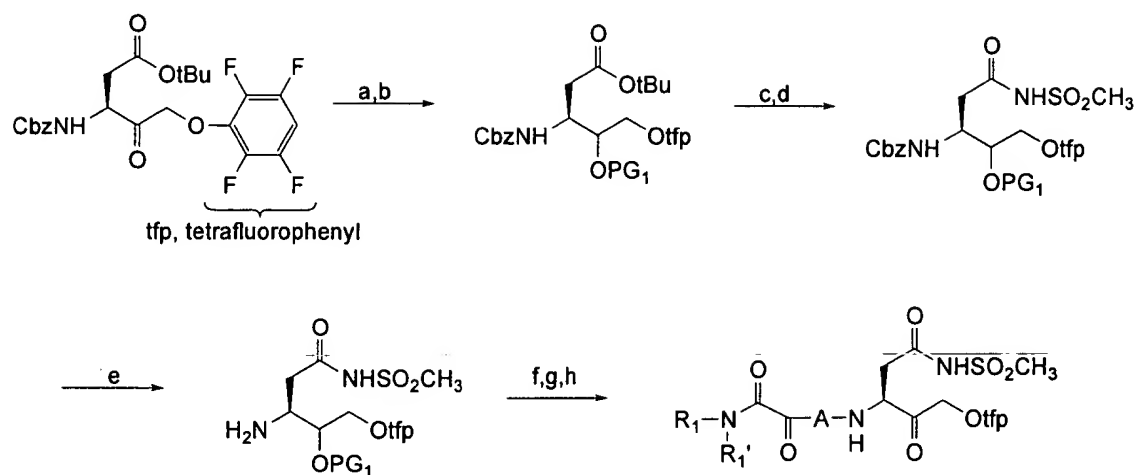
- Starting from the readily available intermediate, modified by addition of
- 5 tetrafluorophenyl, the t-butyl ester is hydrolyzed, followed by coupling with methyl sulfonamide (or other substituted sulfonamide). Acid-catalyzed ketal formation using ethanol is assisted by cyclization of the sulfonamide to form a stable 5-membered ring. The carbobenzyloxy urethane is then removed, the aspartyl intermediate coupled to the substituted oxamyl peptide of choice, then the ketal deprotected. (a) TFA, anisole, CH₂Cl₂, RT; (b) EDCl, DMAP (cat.), CH₃SO₂NH₂, CH₂Cl₂, RT; or i. CDI; ii. CH₃SO₂NH₂, DBU, 0°C; (c) Ethanol, CH(OEt)₃, p-TsOH, toluene reflux; (d) H₂; Pd/C, RT; 10 (e) R₁(R₁')NCOCONH(amino acid)CO₂H, EDCl, HOBT, N-Me Morpholine, CH₂Cl₂, 0°C-RT; (f) TFA, anisole, CH₂Cl₂, H₂O, RT.

Scheme 3d



- Starting from the readily available intermediate, modified by addition of
- 5 tetrafluorophenyl, the t-butyl ester is hydrolyzed, followed by coupling with methyl sulfonamide (or other substituted sulfonamide). Acid-catalyzed ketal formation using ethanol is assisted by cyclization of the sulfonamide to form a stable 5-membered ring. The fluorenylmethyloxy urethane is then removed, the aspartyl intermediate coupled to the substituted oxamyl peptide of choice, then the ketal deprotected. (a) TFA, anisole, CH_2Cl_2 , RT; (b) EDCl , DMAP (cat.), $\text{CH}_3\text{SO}_2\text{NH}_2$, CH_2Cl_2 , RT; (c) Ethanol, $\text{CH}(\text{OEt})_3$, p-TsOH, toluene reflux; (d) Et_2NH , DMF, RT; (e) $\text{R}_1(\text{R}_1')\text{NCOCONH(amino acid)CO}_2\text{H}$, EDCl , HOBt, N-Me Morpholine, CH_2Cl_2 , 0°C -RT; (f) H_2 ; Pd/C, RT.
- 10

Scheme 3e



Starting from the readily available intermediate, modified by addition of

5 tetrafluorophenyl, the ketone is reduced and protected. The t-butyl ester is hydrolyzed followed by coupling with methyl sulfonamide (or other substituted sulfonamide). The carbobenzyloxy urethane is then removed, the aspartyl intermediate coupled to the substituted oxamyl peptide of choice. The alcohol protecting group is then removed, and oxidation yields the cpd fitting formula (a) i. ICBF, NMM; ii. NaBH₄; (b) TBDPSCl imid,

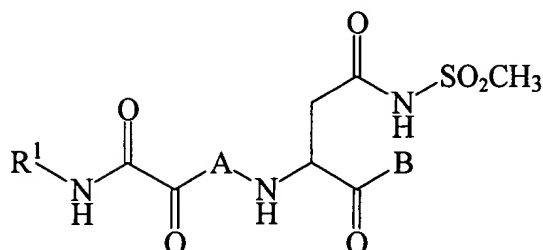
10 CH₂Cl₂; (c) p-TsOH, toluene reflux; (d) i. CDI, THF; ii. H₂NSO₂CH₃, DBU; (e) H₂; Pd/C, RT; (f) R₁(R₁')NCOCONH(amino acid)CO₂H, EDCl, HOBt, N-Me Morpholine, CH₂Cl₂, 0°C-RT; (g) TBAF, THF; (h) Dess Martin periodinane, CH₂Cl₂.

EXAMPLE 7

REPRESENTATIVE COMPOUNDS

The representative compounds listed in the following Table 2 were made according to the procedures set forth above in Examples 2 or 3.

Table 2
Representative Compounds



5

Cpd	A	B	R ¹	Formula	MW	MS(ES) Neg.
75	NHCH(CH ₃)CO	CH ₂ O(2,3,5,6-tetraF-Ph)	(2-t-Bu)Ph	C ₂₇ H ₃₀ F ₄ N ₄ O ₈ S	646.62	645.28
118	NHCH(CH(CH ₃) ₂) CO	H	(2-t-Bu)Ph	C ₂₂ H ₃₂ N ₄ O ₇ S	496.20	495.37
120	NHCH(CH(CH ₃) ₂) CO	H	(2-PhCH ₂)Ph	C ₂₅ H ₃₀ N ₄ O ₇ S	530.60	529.32
128	NHCH(CH(CH ₃) ₂) CO	H	(2-Br)Ph	C ₁₈ H ₂₃ Br N ₄ O ₇ S	518.05	519.22
130	NHCH(CH ₃)CO	H	(2-Br)Ph	C ₁₆ H ₁₉ Br N ₄ O ₇ S	491.32	491.09
131	NHCH(CH ₃)CO	H	(2-t-Bu)Ph	C ₂₀ H ₂₈ N ₄ O ₇ S	468.53	467.26
132	NHCH(CH ₃)CO	H	(2-PhCH ₂)Ph	C ₂₃ H ₂₆ N ₄ O ₇ S	502.55	501.27

EXAMPLE 8

ACTIVITY OF REPRESENTATIVE COMPOUND

10

The activity of a representative compound of this invention (*i.e.*, Compound No. 1) was evaluated according to the procedures disclosed in Example 1. More specifically, the equations set forth in Example 1 were used determine the K_i values of

inhibitor (*i.e.*, Compound No. 1) bound to a ICE/ced-3 family protease. A continuous assay was run for sixty minutes at various concentrations of the inhibitor and the substrate. The assay was formulated essentially the same as described in Example 1, except that the reaction was initiated by adding the enzyme to the substrate-inhibitor mixture. The K_i values were obtained by simulating the product AMC formation as a function of time according to Equation 1. The results of this assay are set forth below in Table 1, wherein the reference compound was Cbz-ValAlaAsp-CH₂F

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Table 2

Cpd. No.	mICE K _i (μM)	CPP32 K _i (μM)	MCH-2 K _i (μM))	MCH-5 K _i (μM)
1	0.004	0.856	0.681	0.011
reference	0.015	0.820	0.594	0.018

5 Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

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